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VOLUME 56  
1946

PUBLISHERS  
AMERICAN MEDICAL ASSOCIATION  
CHICAGO, ILL.



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## OBSERVATIONS IN A CASE OF MUSCULAR DYSTROPHY, WITH REFERENCE TO DIAGNOSTIC SIGNIFICANCE

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**D**ISEASES affecting the muscular system may present difficulties in diagnosis, particularly when they are characterized by atrophy of the muscles. For example, there are striking similarities in the course, signs and symptoms of the late dystrophy of distal type (Gowers) and of progressive muscular atrophy. The former belongs to the group of diseases which may best be described as the primary myopathies, or muscular dystrophies, and the latter to the so-called secondary myopathies.

In the primary muscular diseases, such as progressive muscular dystrophy, the pathologic process is thought to begin within the muscle fibers themselves, the changes result in weakness and paralysis in the presence of an apparently normal motor nerve. In the so-called secondary myopathies, the basic lesion lies within the spinal cord or the peripheral nerve, and the atrophy of the muscle is dependent on changes within the lower motor neuron.

It is possible that histologic examination might throw light on the course of the muscular dystrophies and, moreover, help to establish a diagnosis in some cases. The possibility of histologic differentiation of these two groups of diseases has been denied by Durante<sup>1</sup> (1902), but many authors do not accept this view. Among those who have described characteristic changes in dystrophic muscles are Pappenheimer,<sup>2</sup> Slauck<sup>3</sup> and Hassin.<sup>4</sup>

In this paper a further attempt is made to define the histologic differences between the primary and the secondary myopathies.

From the Nuffield Department of Orthopaedic Surgery (Miss Bowden) and the Department of Zoology and Comparative Anatomy (Mr Gutmann), Oxford University.

1 Durante, G. Anatomie pathologique de muscles, in Cornil, V, and Ranvier, L. Manuel d'histologie pathologique, Paris, F Alcan, 1902, vol 2, p 1.

2 Pappenheimer, A M. Beitr z path Anat u z allg Path 44 430, 1908.

3 Slauck, A. Pathologische Anatomie der Myopathien, in Bumke, O, and Foerster, O. Handbuch der Neurologie, Berlin, Julius Springer, 1932, vol 16, p 412.

4 Hassin, G B. J Neuropath & Exper Neurol 2 315 1943.

## METHOD

Two cases are described in which weakness was first noticed in the muscles of the lower extremities. Specimens of muscle were taken for biopsy and fixed immediately in a 5 per cent concentration of official solution of formaldehyde in isotonic solution of sodium chloride. Frozen sections were cut and stained with Gros's modification of the Bielschowsky method (for the determination of nerve fibers), hematoxylin and eosin and sudan III. Part of the specimen was embedded in paraffin, and the sections were stained with hematoxylin and eosin and with Mallory's phosphotungstic acid stain.

## REPORT OF CASES

**CASE 1—History**—The patient was a man aged 42. On direct questioning, he admitted having noticed a slight loss of strength some time before October 1939. In November 1939, in the course of treatment for a simple fracture of the left ankle, drop foot was noticed by the physician. Electrotherapy improved the power of the weak muscles. During 1943 the hands became weak, and the patient had



Fig 1—Apathetic facial expression (myopathic facies)

difficulty in carrying weights and finally was unable to pull the trigger of a rifle with the right forefinger. In November 1943 there was sudden onset of pain in the left calf, related to exercise; subsequently, the pain became less severe. It was usually precipitated by walking but was not increased if he continued with exercise. There was no deterioration in power as the day went on. No dysphagia, diplopia or ptosis, no sphincter disturbance, and no loss of weight, dyspnea or anorexia was noted.

**Past History**—The past history revealed nothing significant.

**Family History**—There was no family history of a condition similar to the patient's. The patient had 2 normal boys, aged 11 and 13 years.

**Examination**—**Cranial Nerves**. The facial expression (fig 1) was apathetic, with weakness of orbital muscles and paralysis of the upper lip. Otherwise nothing abnormal was detected. The external ocular movements and the pupillary reactions were normal.

**Spinal Nerves**. There was generalized weakness of all muscle groups, including those of the trunk. The distal muscles were more affected than the proximal

ones, and the left leg was involved more than the right. There was bilateral paralysis of the latissimus dorsi and tibialis anterior muscles. Fasciculation was not visible.

**Electrical Reactions** Tested with Bauwens's<sup>5</sup> machine, using stimuli of 1/1,000, 1/50 and 1 second duration, the threshold stimulus was measured in milliamperes. The muscles of the peroneal groups responded normally.

Muscle	Duration, Sec		
	1/1,000	1/50	1
Tibialis Anterior			
Right	No response at 40 ma	No response at 40 ma	At 16 ma sluggish contraction
Left	At 40 ma small localized flicker	Nil	At 11.5 ma sluggish contraction

**Electromyographic Study** Both the right and the left tibialis anterior muscle showed only a few motor unit action potentials, some of which were polyphasic

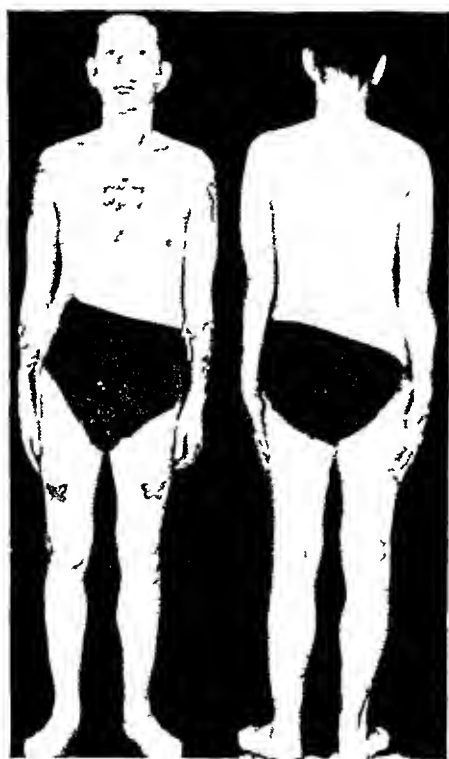


Fig. 2 (case 1) —Weakness of the abdominal muscles and absence of conspicuous localized wasting of the muscle groups.

and of low amplitude. In addition, action potentials which were indistinguishable from those of fibrillation were present in the right tibialis anterior muscle.

**Reflexes** The reflexes were brisk in the upper limb. The abdominal reflexes were present. The knee jerks were brisk and equal on the two sides. The ankle jerks were absent. Plantar responses were of flexor type.

**Sensation** There was no demonstrable sensory loss.

**Clinical Diagnosis**—The clinical diagnosis was muscular dystrophy of late onset. The interesting features of the case were the late onset of disease, the absence of a family history of a similar disorder and the finding of action potentials resembling those of fibrillation. Records of isolated cases of progressive

muscular dystrophy of late onset are not numerous in the literature, and the symptoms are varied, but cases similar to this one have been described (Nevin<sup>6</sup>)

*Biopsy*—On Dec 15, 1943 specimens of muscle from the left leg were taken for biopsy, with local anesthesia. The muscles were stimulated directly, using an induction coil and two needle electrodes. The peroneal muscles were rather pale but contracted briskly with a stimulus of 185 volts. The tibialis anterior and extensor digitorum longus muscles were exceedingly pale and fatty looking. With a stimulus of 5 volts a massive, sluggish and undulating response was obtained.

*Progress* (Oct 20, 1944)—The patient complained of increasing generalized weakness, he found it difficult to run or hurry and his appetite was deteriorating, but there was no other change in the symptoms.

Weakness of the trunk muscles was more marked, the abdomen protruded, and there was postural kyphosis (fig 2). There was no further paralysis, although generalized weakness was more noticeable. There was no obvious wasting of the small muscles of the hand (fig 3).



Fig 3 (case 1)—Absence of wasting of the intrinsic muscles of the hand

*Electromyographic Study*—Right and Left Tibialis Anterior Muscles. The motor unit action potentials were polyphasic and of low amplitude. There was only doubtful fibrillation irritability on insertion of the concentric needle electrode, but there were some action potentials indistinguishable from those of fibrillation (fig 4).

Right Latissimus Dorsi Muscle. Motor unit action potentials, of the same type as those seen in the tibialis anterior, were present. No fibrillation or fibrillation irritability was found.

Left Flexor Carpi Ulnaris Muscle. Motor unit action potentials were found, with some action potentials indistinguishable from those due to fibrillation irritability.

*Histologic Observations*—Examination of the four biopsy specimens (taken on Dec 15, 1943) showed varying degrees of atrophic change. The disease had apparently started at different times in the muscles, and thus an opportunity of observing the progress of the pathologic process was provided.

Atrophy was slight or absent in the peroneus longus and more advanced in the extensor digitorum longus muscle, and in the two specimens of the tibialis anterior muscle it was of extreme degree

**Peroneus Longus** There was a slight increase of fat and connective tissue between the muscle fibers. There was no indication of atrophy, the average diameter of the muscle fibers was 40 microns

Cross striation was clearly visible, and there was no hyaline or fatty degeneration. There was apparently an increase in the muscle nuclei (fig 5A). The nuclei were arranged in rows and sometimes in clumps (fig 5B), an arrangement which is not found in normal muscle fibers. Often the nuclei were clustered in pairs, and this was especially conspicuous near the capillaries (fig 5C). No mitotic figures were seen, and there was no increase in the number of the nucleoli, such as can be found in early stages of denervation atrophy. The nuclei had one, and rarely two, nucleoli. Around many of the nuclei a halo of small granules was found (fig 5D). These were clearly visible in sections stained with silver but were not apparent in hematoxylin-eosin preparations. In normal muscle fibers granules are found regularly distributed at the level of the Q bands. Such granules were also observed in this muscle, but they were usually restricted to a narrow zone of the fiber close to the nucleus. This alteration in staining reactions and distribution of the granules is not explained, but it does suggest that some pathologic change may have taken place in the sarcoplasm of the muscle fibers

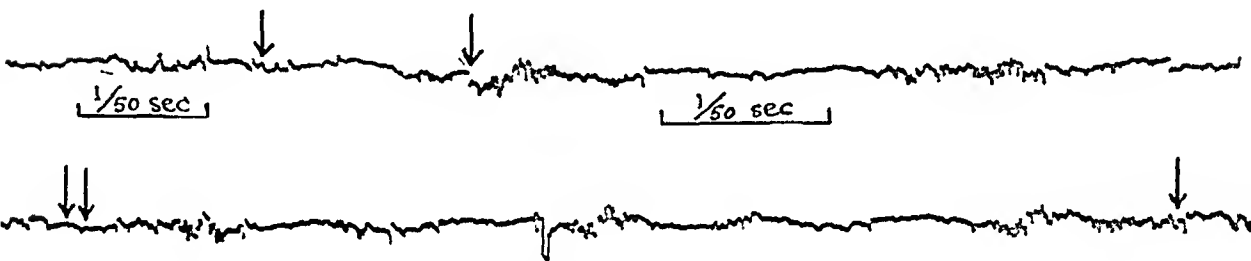


Fig 4 (case 1) —Electromyographic tracings from the tibialis anterior muscle (during maximum voluntary effort), showing the bizarre, highly polyphasic motor unit action potentials and the spikes indistinguishable from action potentials characteristic of fibrillation, the latter being marked by arrows

No empty nerve trunks were seen. The fibers were thick and myelinated. The pattern of innervation was normal. The terminal branches innervating the end plates lay near to the main trunks (fig 5E). No abnormality was found in the nuclei of the endplates.

**Extensor Digitorum** There was a slight degree of atrophy, with some increase of fat and connective tissue between the muscle fibers. Many of the fibers were rather thick, some being even larger than normal (diameters of 90 microns were found), but there were also groups of rather thin muscle fibers. Some fibers were very large, appeared swollen and showed many spaces, with loosening of the compact arrangement of the fibrils. Cross striation was still clearly visible. There was an apparent numerical increase of the nuclei, for the muscle fibers appeared to be packed with them. Some of the nuclei were arranged in long rows, and in other parts there were large clumps of nuclei (fig 5F), often surrounded by fine granules. In silver preparations round or oval vacuoles were occasionally found between these clumps (fig 5G). They were represented by pale circles, surrounded with a halo of granules. Some of these vacuoles were about twice the size of the neighboring nuclei, but on an average they were of about equal size.



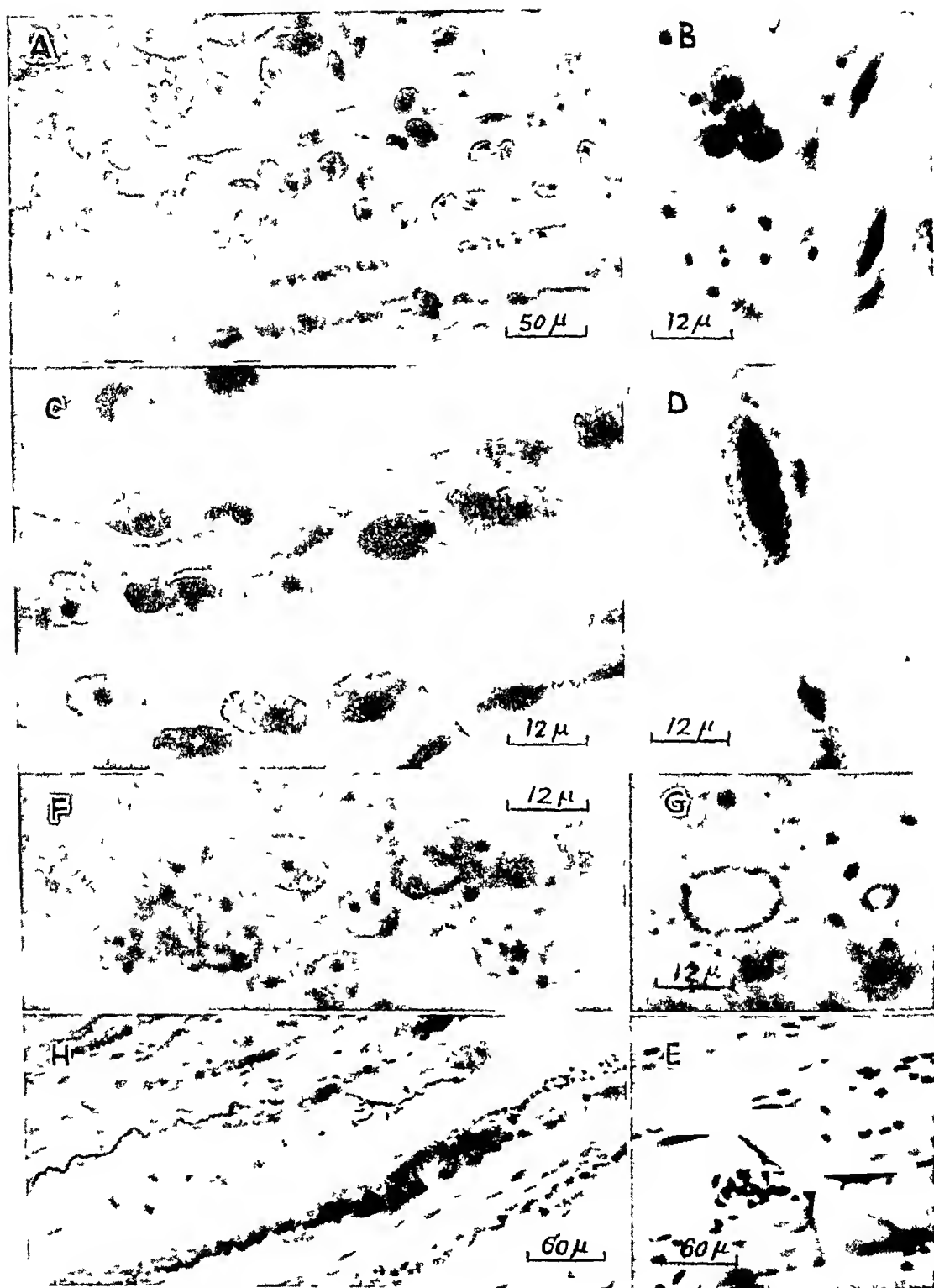


Figure 5

*(See legend on opposite page)*

**Tibialis Anterior** The muscle showed an extreme degree of atrophy. A large part of it was replaced by connective tissue and fat. Scattered in the connective tissue were remnants of the muscle fibers, some thin and crowded with nuclei, others consisting of very large fragments filled with unstriated and apparently degenerated material (figs 5 *H* and 6 *A*). However, it seemed that the muscle fibers had not all been attacked simultaneously, and some were still of fairly large diameter and the cross striation was intact. Some of these fibers showed a centrally placed row of nuclei arranged in long bands (fig 6 *B*). Around these rows or clumps of nuclei there was often a clear halo, but the more peripheral part of the muscle fibers still showed cross striation (fig 6 *C*). In some fibers fibrillary disruption was proceeding, in others there was only a peripheral mantle of striated fibrils around a clear central zone, and in others unstriated fibrils embedded in a granular material were just detectable (fig 6 *D* and *E*). These changes possibly represent stages in the dedifferentiation of the protoplasm of the muscle fibers. Several muscle fibers were represented by tubes filled with pyknotic nuclei clustered tightly together (fig 7 *B*), others contained in addition distinct eosinophilic masses, usually in the form of droplets (fig 6 *F*). In such fibers hyaline degeneration seemed to be occurring. Many fibers, of varying size, were filled with irregularly distributed granules and groups of small nuclei. It was apparently in these fibers that fragmentation occurred (fig 7 *A*). This fragmentation seemed to be the latest stage of the atrophy, intermediate stages could be found in which pieces of muscle fiber were still connected by fine strands. The same appearance is found in the late stages of denervation atrophy (Bowden and Gutmann 7).

The nuclear changes were a striking feature of these dystrophic muscles. There might be an aggregation of nuclei, usually of uniform size. The majority were small and pyknotic and lay together in clusters, some showed signs of breakdown of chromatin. In others only the nuclear membrane stained darkly and irregularly (fig 7 *C*), or a pale shadow might be all that was left (fig 6 *E*). Around single nuclei or groups of nuclei clear halos often appeared (fig 7 *D*). Two or three pyknotic nuclei might be surrounded by a clear zone, others were clustered in groups, or there were large, featureless pyknotic masses, probably formed by the coalescence of several nuclei. Finally, fragments of nuclear remains could be seen, and these were apparently undergoing ultimate dissolution.

**Innervation**—There were no empty nerve trunks. In the larger trunks the nerve fibers were thickly myelinated, but in the individual Schwann tubes the

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7 Bowden, R. E. M., and Gutmann, E. *Brain* 67 273, 1944

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#### EXPLANATION OF PLATE

Fig 5 (case 1) —*A* to *E*, musculus peroneus longus. *A*, muscle fibers crowded with nuclei, arranged in rows or clumps, *B*, muscle fiber with clumps of nuclei, *C*, nuclei arranged in pairs along the capillaries, *D*, muscle fiber with a halo of granules surrounding the nucleus, *E*, muscle fiber showing normal pattern of innervation.

*F* and *G*, musculus extensor digitorum, showing (*F*) many small nuclei arranged in clumps and (*G*) nuclei arranged in a cluster around a vacuole.

*H*, musculus tibialis anterior, showing extreme degree of atrophy of the muscle with many thin muscle fibers crowded with nuclei and some large fragments of muscle fibers with no cross striation. The nerve fibers run for long distances between and along the muscle fibers.

In this figure, and in figures 6, 7 and 8, all sections are of muscle stained with the Bielschowsky method except where otherwise indicated.

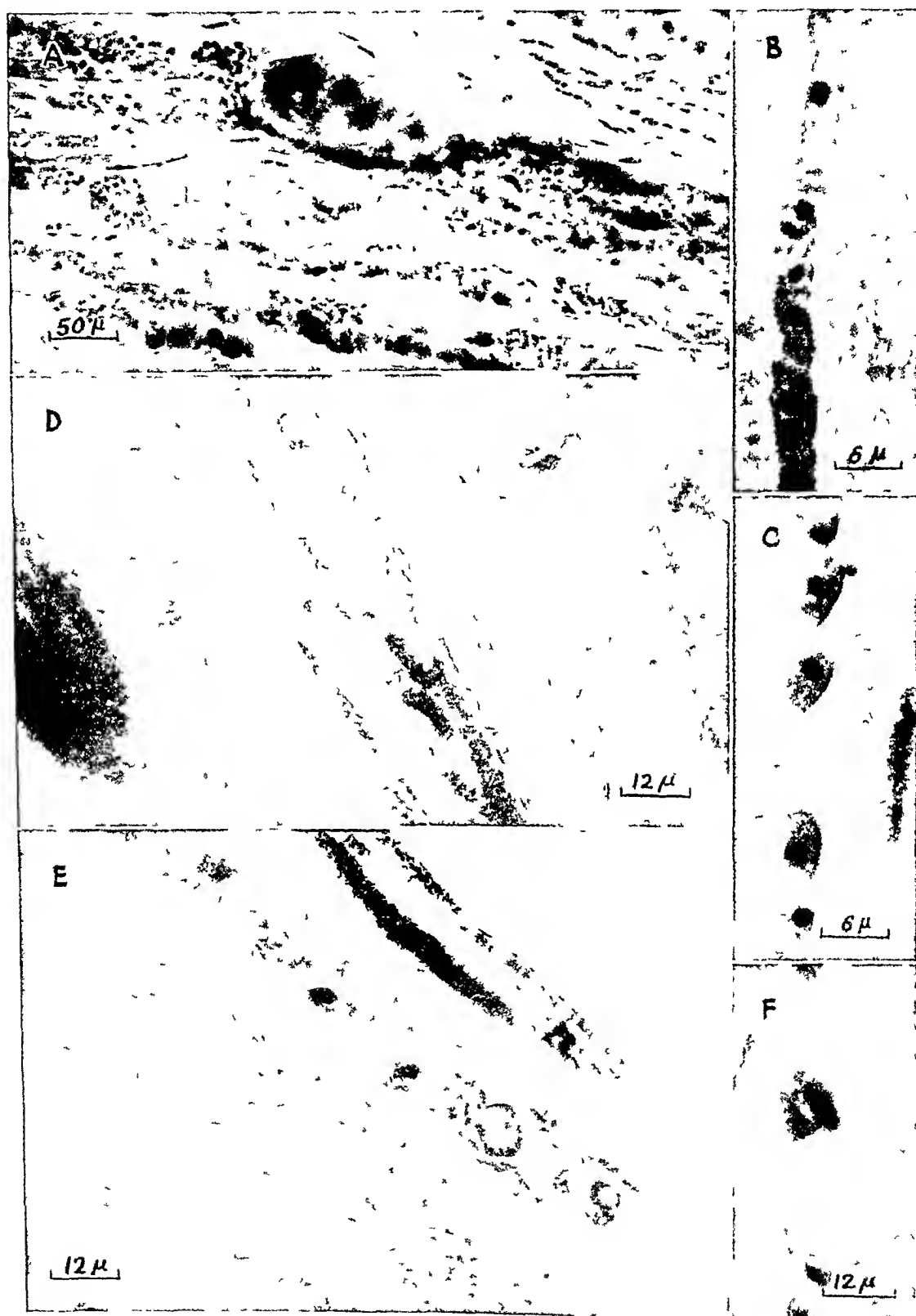


Figure 6

*(See legend on opposite page)*

diameter of some fibers was rather small in relation to that of the tube. The axon occasionally branched, and these branches ran along or across the muscle fiber or within the connective tissue, forming terminal knobs, such as are seen when regeneration of the axon has occurred (Gutmann and Young<sup>8</sup>) (fig 8A). Small rings (fig 8B) or large end bulbs (fig 8C and D) were seen on the surface of the muscle fibers or within the connective tissue. This pattern of innervation is not found in normal muscle but is typical of muscle reinnervated after some delay (Gutmann and Young<sup>8</sup>). The picture resembles abortive regeneration of nerve fibers.

*Comment*—We may now attempt to reconstruct the sequence of changes in this case of progressive muscular dystrophy. The pathologic process is first indicated by the reaction of the nuclei and the granular constituents of the sarcoplasm. The muscle fibers appear crowded with nuclei which are arranged in long rows or clumps. The reaction of the sarcoplasm is indicated by the appearance of granules, either in longitudinal zones or in a halo around some of the nuclei. At this stage there are no demonstrable degenerative changes in the nerve trunks or the nerve endings. In later stages there is a further increase of nuclear agglomerations, some of the nuclei become pyknotic, and later the chromatic material is dissolved. A striking feature, best seen in silver preparations, is the appearance of vacuoles between groups of nuclei. The process does not begin simultaneously in all muscle fibers. Muscle fibers with intact cross striation and large, bloated nuclei may be seen side by side with fragments of fibers represented by sarcolemmal tubes filled with clumps of pyknotic nuclei. The break-up of the muscle fibers appears to begin in the region of single or agglomerated nuclei, around which clear halos may be seen where the cross striated material has been destroyed. It may be that these spaces and the fragmentation of the fibers are caused by a lytic substance freed by the nuclei. Continuity of the muscle fibers is further lost by longitudinal splitting. Remnants of muscle fibers are found represented only

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8 Gutmann, E, and Young, J. Z. *J. Anat.* 78: 15, 1944.

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#### EXPLANATION OF PLATE

Fig 6 (case 1)—Musculus tibialis anterior. A, extreme degree of atrophy of the muscle. Note large fragments of muscle tissue filled with unstriated material. B, muscle fiber in which the nuclei are arranged in a central row. C, muscle fiber with a central row of nuclei surrounded by a clear halo, only the peripheral mantle showing cross striated fibrils.

D, the different states of the muscle fibers. One muscle fiber is in process of fibrillary disruption, another shows a central halo with a peripheral mantle of striated fibrils. (Mallory's phosphotungstic acid hematoxylin stain.)

E, different states of the muscle fibers. One muscle fiber shows intact cross striations, another contains only a few fibrils and nuclei in the process of breakdown of the chromatin, another shows just a few unstriated fibrils embedded in granular material. (Mallory's phosphotungstic acid hematoxylin stain.)

F, muscle fiber containing a droplet of hyaline degenerated material between pyknotic nuclei. (Hematoxylin and eosin.)

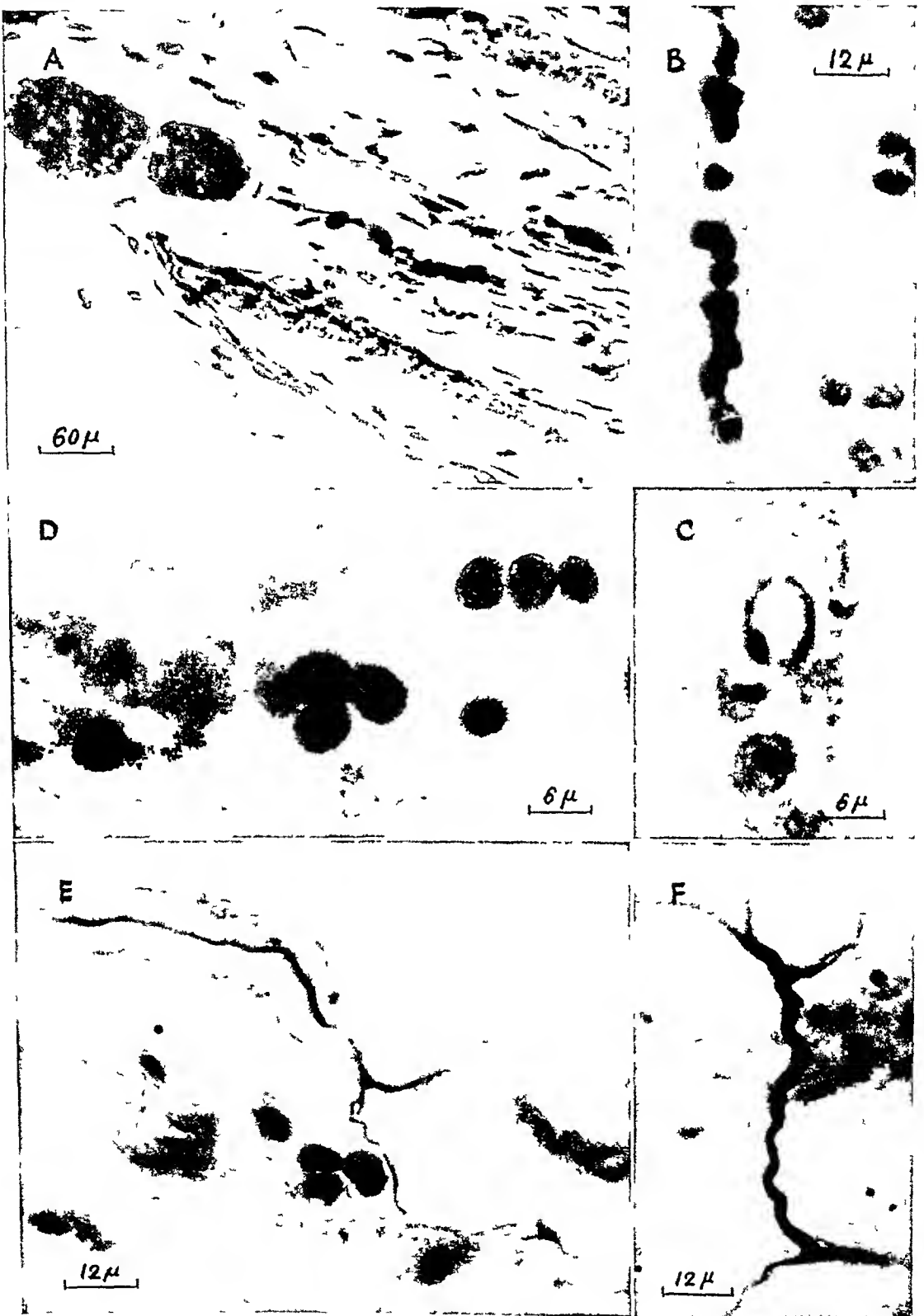


Figure 7

*(See legend on opposite page)*

by a thin band with a few nuclei and granules and with fibrils splitting up in all directions

It is interesting to note that even in the latest stages cross striation of the thinnest muscle fibers may be intact, but it cannot be detected in fragments which are filled with irregularly distributed granules and disintegrating nuclei. In such fibers the cytoplasm apparently undergoes far reaching, and probably irreversible, changes, which appear to lead to loss of contact of the nerve with muscle fiber. If we may assume that the pathologic change leads to a disturbance at the myoneural junction and that the nerve fibers grow out again in an attempt to form new contacts, it is possible to explain the changes which present the picture of abortive regeneration of the nerve fibers.

There is no sign of degeneration in the larger nerve trunks, or of any previous degeneration, which would be indicated by an increase of the Schwann cells in these trunks. Moreover, the long "escaped fibers" running between the muscle fibers are often naked axons, which can be traced to a nerve fiber within a Schwann tube. Thus it is clear that in progressive muscular dystrophy the pathologic changes in the muscle fibers are primary and lead to a disturbance at the myoneural junction and to loss of contact of the nerve fibers. The terminal axons grow out farther in an attempt to form new contacts, but the changes in the muscle fibers are usually too far advanced to allow successful reinnervation.

Since there are obvious differences between the so-called primary and secondary myopathies, histologic examination of the muscle is likely to be of value both in diagnosis and in classification.

In a comparison of the primary and the secondary myopathies, two questions have to be considered: 1. Where do the pathologic changes in progressive muscular dystrophy begin, and what is the sequence of events? 2. Are the histopathologic changes in the dystrophies specific and therefore distinguishable from those of the secondary myopathies?

1. **Histologic Observations.** Histologic studies suggest that the first reaction to an unknown pathologic agent is one of the nuclei and the granular constituents of the sarcoplasm. The nuclei react with an apparent numerical increase, and they form rows and clumps, which are not found in normal muscles. There is no increase in the number

#### EXPLANATION OF PLATE

Fig. 7 (case 1)—*Musculus tibialis anterior*. *A*, extreme degree of atrophy. A muscle fiber filled with irregularly distributed granules is seen in the process of fragmentation. *B*, muscle fiber filled with clumps of pyknotic nuclei (Hematoxylin and eosin). *C*, part of a muscle fiber with one nucleus showing breakdown of the chromatin. *D*, groups of nuclei surrounded by clear halos. *E*, single Schwann tube containing a nerve fiber which branches off and runs along a muscle fiber. *F*, nerve fiber running across the muscle fiber.

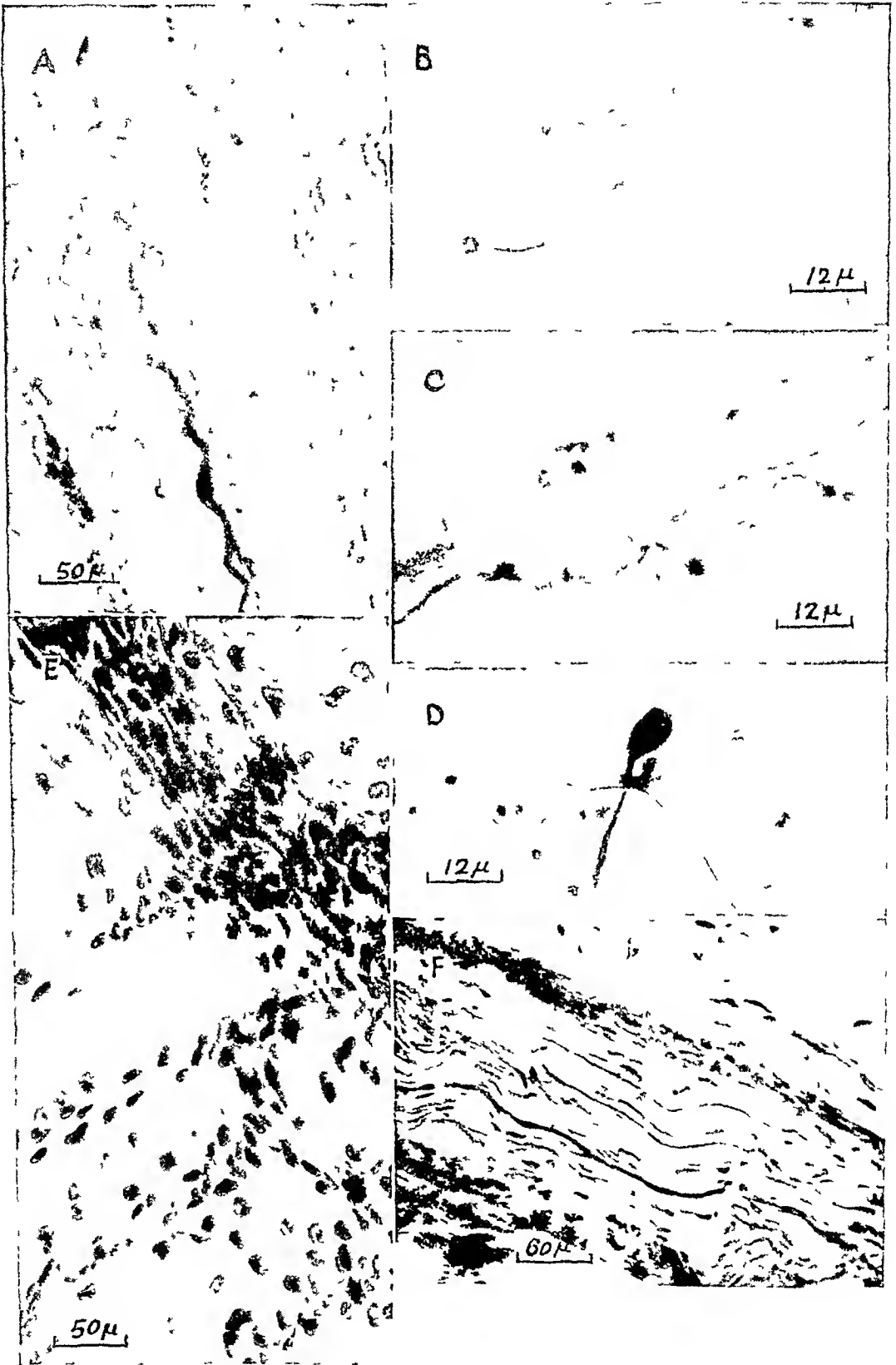


Figure 8

(See legend on opposite page)

of nucleoli, such as is found in denervations. In these early stages of the disease the muscle and nerve fibers show no pathologic changes. There is no indication that the process starts in the interstitial tissues, as suggested by Babes and Marinesco.<sup>9</sup> In the early stages the nuclear reaction is conspicuous, but there is no inflammatory reaction or increase in the connective tissue. Erb<sup>10</sup> described hypertrophic muscle fibers as typical of the early stages of the disease. These observations led him to the conclusion that the disease begins with hypertrophy of the muscle fibers, which is followed by atrophic changes. No definite confirmation of this assumption was found in the present case, though it was not one of pseudohypertrophic muscular dystrophy. In the later stages the nuclei undergo changes leading to their dissolution, and this process is accompanied by fragmentation and ultimate replacement of the muscle fibers with connective tissue. The onset and course of the process vary in the different muscle fibers. Thus, thin muscle fibers with intact cross striation and nuclei may be found side by side with large fragments of muscle filled with irregularly distributed granules and clumps of nuclei. Pyknosis and clustering of the nuclei, dissolution of the chromatin and formation of vacuoles are stages which seem to be significant.

The agglomeration of the nuclei in rows or clumps has been described by most authors. Lewin<sup>11</sup> described the "proliferating nuclei" as "myophages" and referred to their "phagocytic function." He stated that these myophages invade and destroy the contractile substance, forming lacunas or irregular spaces, which may contain fragments of striated material. This material could also be seen within the myophages themselves. Lewin, and afterward Pick,<sup>12</sup> identified the "myophages" with Kollikers osteoclasts.

It is, however, necessary to distinguish the halos and lacunas which are formed around single pyknotic nuclei, or around clumps of them, from the vacuoles appearing between the nuclear masses. There is

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9 Babes and Marinesco, cited by von Meyenburg<sup>15</sup>

10 Erb, W. *Deutsche Ztschr f Nervenhe* **1** 173, 1881

11 Lewin, A. *Deutsche Ztschr f Nervenhe* **2** 139, 1892

12 Pick, F. *Deutsche Ztschr f Nervenhe* **17** 1, 1900

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#### EXPLANATION OF PLATE

Fig 8 (case 1) — *A* to *D*, musculus tibialis anterior. *A*, nerve fiber running for a long distance between the muscle fibers and within the connective tissue. Note the terminal knob. *B*, nerve fiber ending on a muscle fiber, with knobs and end rings. *C*, nerve fibers running along a capillary and ending in knobs. *D*, nerve fiber ending on a muscle fiber with a thick end knob, characteristic of a regenerated nerve fiber.

*E* and *F* (case 2), musculus peroneus longus, showing (*E*) a denervated muscle with empty Schwann tubes and end plates, and (*F*) nerve trunks containing a few thin, apparently regenerated nerve fibers.



no indication that the nuclei invade the muscle fibers, but halos or lacunas undoubtedly appear around them. Here the cross striated fibrils are destroyed, possibly by a lytic agent from the pyknotic and fragmenting nuclei. This is a very late stage, which ultimately leads to fragmentation of the muscle fibers. At an earlier stage small vacuoles appear between masses of the nuclei, and it is possible that they are a product of hyaline degeneration.

It is interesting to note that even with advanced changes cross striation of the thinnest muscle fibers may be intact, but it cannot be detected in fragments which are filled with irregularly distributed granules and disintegrating nuclei. In such fibers the constitution of the cytoplasm apparently undergoes far reaching, and probably irreversible, changes, which lead to loss of contact of the nerve with muscle fibers.

Few authors seem to have studied the nerve fibers in dystrophic muscles. Pappenheimer<sup>2</sup> found no changes in the intramuscular nerve fibers. This is true in the early stages, but in later stages the progressive changes in the muscle fibers lead apparently to a disturbance at the point of contact. Although the axons grow out in an attempt to form new contacts, in view of the advanced changes in the muscle fibers, this attempt may not always be successful.

The finding of action potentials characteristic of fibrillation is significant (fig 4). Such an observation has not been recorded previously in cases of muscular dystrophy. However, the histologic changes offer a possible explanation. The pathologic alterations do not occur simultaneously in the different muscle fibers, and therefore detection of the action potentials of characteristic fibrillation may be difficult.

Polyphasic motor unit action potentials are occasionally observed in normal muscles, but they occur most frequently during reinnervation (Weddell, Feinstein and Pattle<sup>13</sup> and Bowden<sup>14</sup>). Their presence may represent the successful reinnervation of some muscle fibers. The action potentials in the tibialis anterior (fig 4) were of low amplitude, and it is noteworthy that they were of bizarre shape and that, although they were polyphasic they were not exactly similar to those found during reinnervation. These action potentials may represent the electrical activity of grossly abnormal muscle fibers. Another possibility is that this activity originates in fibers which are abnormally scattered in space, and a third is that, owing to the disease process, the fibers of the single motor unit are not acting synchronously. Histologic observations lend

13 Weddell, G., Feinstein, B., and Pattle, R. E. *Lancet* 1: 236, 1943, *Brain* 67: 221, 1944.

14 Bowden, R. E. M. Unpublished material.

support to the first suggestion but do not exclude the others. Further observations on this point are necessary.

We may conclude that progressive muscular dystrophy is a primary myopathy, as suggested by Durante, Friedreich and Lichtheim. Some authors have described changes in the spinal cord, and this observation would point to a central origin. But these lesions were on the whole not considered commensurate with the intensity and the extent of the changes in the muscles (Hassin<sup>1</sup>). Moreover, most of the authors have found no pathologic change in the nerve cells (von Meyenburg<sup>15</sup>).

2 Histologic Differentiation of Primary and Secondary Myopathies. That there are changes typical of dystrophic muscles has been stated by some authors. The observations reported in this paper were made in only 1 case of muscular dystrophy, however, the features were so striking that a distinction between the two types of disease could be made easily. Study of more material is, of course, necessary. Kure and associates<sup>16</sup> claimed to have produced dystrophic changes experimentally in muscle after severance of the sympathetic nerve trunk. The essential changes which they thought characteristic of progressive muscular dystrophy were as follows: great differences in size of muscle fibers, appearance of some hypertrophied fibers, increase of interstitial tissue, appearance of rounded muscle fibers and formation of vacuoles in the muscle fibers. None of these changes can be considered specific (in 1 case these changes were described by Kure and his associates only seven days after sympathectomy), and there is neither any evidence of the mechanism which they suggested nor any possibility of distinguishing progressive muscular dystrophy by these criteria.

Slauck<sup>3</sup> contrasted the arrangement of the muscle fibers in the two conditions, the fibers are irregularly distributed without grouping into bundles in cases of dystrophy, while in cases of denervation atrophy they are grouped in bundles. He also described the destruction of the muscle fibers by the "endogenous," more centrally placed, nuclei in cases of dystrophy and contrasted this with the destruction of the fibers by subsarcolemmal nuclei in cases of denervation atrophy (Slauck<sup>4</sup>). However, he did not state what stages of denervation were observed and compared. Comparison of dystrophic muscle with muscle in the late stages of denervation atrophy does not allow such a clearcut distinction.

15 von Meyenburg, H. Die quergestreifte Musculatur, in Henke, F., and Lubarsch, O. Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1929, vol. 9, pt. 1.

16 Kure, K., Hatano, S., Shinosaki, T., and Nagano, T. Ztschr. f. d. ges. exper. Med. 47: 89, 1925.

Homogenization, myofibrillary disruption, myophagia and fatty metamorphosis, with the ultimate formation of a connective tissue scar, have been considered primary degenerative changes independent of the condition of the spinal cord (Hassin<sup>4</sup>) However, in the late stages of denervation atrophy (twenty years of denervation or more) the changes in the muscle are similar to those observed in the late stages of dystrophy Swelling, pyknosis and dissolution of the nuclei, formation of rows, and spherical agglomerations are all noted, in addition to longitudinal splitting, myofibrillary disruption and fragmentation of the muscle fibers Hyaline and vacuolar degeneration of the muscle fibers and extreme increase of fat and connective tissue can be found with both disorders In fact, the picture in the advanced stages of denervation atrophy is essentially the same as that of the muscle fibers in case 1 In denervated muscle the changes leading to fragmentation of the muscle fibers, associated with nuclear dissolution, are seen only in the very latest stages, while they apparently develop much more rapidly in dystrophic muscles In both the process within the muscle fiber ultimately leads to cell death

Thus, we may conclude from the material at our disposal that no clear differentiation between primary and secondary myopathies is possible when the state of the muscle fibers is considered alone However, a distinction can be made when the innervation is observed In cases of muscular dystrophy the changes in the muscle fibers are found while innervation is still intact or a pattern of terminal abortive regeneration is present In cases of atrophy of neural origin denervation is indicated by the empty nerve trunks This fact is demonstrated by the following case

*CASE 2—History*—A boy aged 15 years had gradual onset of pain in the ankles, weakness and clawing of the toes at the age of 13½ years

*Past and Family Histories*—The histories revealed nothing of significance

*Examinations* (Oct 9, 1942)—The patient appeared pale and unhealthy, he was of the asthenic type There was a high stepping gait There were mild kyphoscoliosis of the lower dorsal region and extreme talipes cavovarus of both feet, with clawing of all toes

*Cranial Nerves* There were slight paresis of the right external rectus muscle and an apathetic facial expression Otherwise, nothing abnormal was detected

*Spinal Nerves* There was no localized thickening of the nerve trunks The intrinsic muscles of the hands showed slight wasting The abdominal reflexes were present and brisk In the lower limbs, there were weakness and wasting of the right and left quadriceps muscles (which acted only against gravity) and slight weakness of the hamstrings and the medial popliteal group of muscles Of the lateral popliteal muscles, there was feeble action of the extensor digitorum longus on both sides The right tibialis anterior was barely active, the other muscles were paralyzed Knee and ankle jerks were absent The plantar responses were of flexor type

**Electrical Reactions** Reaction of degeneration was present in the paralyzed muscles, with feeble faradic responses in the paretic muscles

**Sensory Tests** No changes in sensation were noted

**Laboratory Studies** The Wassermann reaction of the blood was negative  
Spinal puncture revealed an initial pressure of 100 mm, with no block The fluid

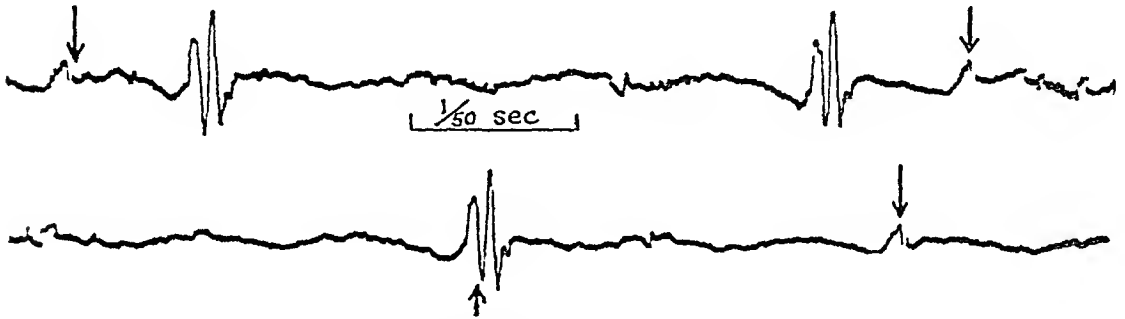


Fig 9 (case 2)—Electromyographic tracing (same calibration as that in figure 4) from the first dorsal interosseus muscle of the right hand during maximum voluntary effort Three normal motor unit action potentials (upward pointing arrows) and action potentials characteristic of fibrillation (downward pointing arrows) are shown



Fig 10 (case 2)—Atrophy of the intrinsic muscles of the right hand, with clawing of the digits

was clear and did not clot The protein measured 200 mg and the chlorides 700 mg, per hundred cubic centimeters The cell count revealed 2 lymphocytes and 1 red cell, per cubic millimeter

**Sweating Test** (Dr Ludwig Guttmann) There was symmetric hyperhidrosis below the knees

**Roentgenographic Study** A roentgenogram of the spine revealed no evidence of spina bifida and no osteochondritis

**Biopsy of Fibular Communicating Nerve** (sensory) (W Holmes)—"The specimen showed no noteworthy abnormalities. There was no degeneration of the axons or of the myelin or hyperplasia of the sheaths and no inflammatory reaction. There was no evidence of neuritis, and the central neurons must have been undamaged, as the axons were intact."

**Electromyographic Study**—The first dorsal interossei muscle of the hand showed both motor unit action potentials and potentials characteristic of fibrillation (fig 9)

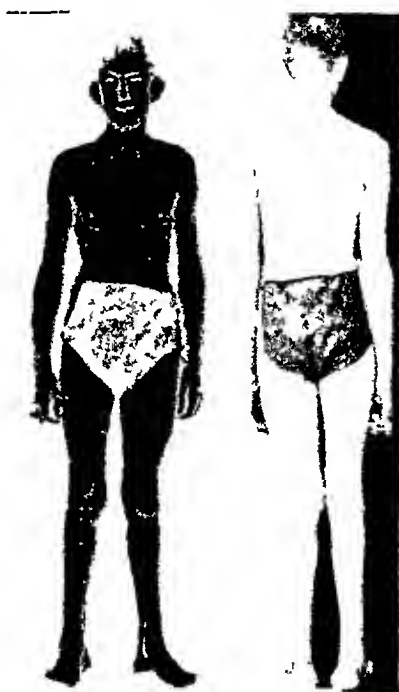


Fig 11 (case 2)—Dorsal kyphoseoliosis, genu valgum and clawing of the feet with varus deformity of the heels. Note the conspicuous wasting of the muscles of the right hand and the distal part of the lower limbs

**Progress**—There were increasing ataxia and weakness, necessitating bilateral arthrodesis of the tarsus (May 19, 1943), and progressive atrophy and weakness of the intrinsic muscles of the hand (figs 10 and 11, taken on Oct 3, 1944)

**Diagnosis**—The diagnosis was peroneal muscular atrophy

**Histologic Observations**—Examination of the peroneus longus showed little atrophic change in the muscle fibers but some increase in connective tissue and fat. There were no nuclear changes resembling those found in case 1, but denervation of some muscle fibers was indicated by an increase in the number of nucleoli. In the subsarcolemmal nuclei, two to four nucleoli were found, as compared with the one or two nuclei seen in normal muscle

The degree of innervation varied in different nerve trunks. A few trunks contained thick, apparently normal fibers. Many empty nerve trunks and empty end plates were found (fig 8E). However, occasionally a nerve trunk contained a few rather thin nerve fibers, indicating early reinnervation of a denervated trunk (fig 8F).

Almost complete denervation had taken place, but the small degree of atrophy indicated that the time of denervation had been short.

The histologic changes show a lesion of the lower motor neuron, but of course do not indicate where this lesion is situated, for the picture in the muscle will be identical whether the cord or the peripheral nerve is affected. However, the level of the lesion can usually be decided by clinical examination. In this case the normal sensation and the normal appearance of the sensory nerve pointed to predominant involvement of the motor nerve cells. It is interesting that there were a few normal nerve trunks and that there were a few containing regenerating fibers. Some anterior horn cells must have been spared, while in others the changes may have been reversible to some extent, thus enabling the cells to send out new axons.

#### SUMMARY

A case of progressive muscular dystrophy is described.

The early changes consist in a reaction of the nuclei and the granular constituents of the sarcoplasm. In later stages there is complete dedifferentiation of the striated material, leading to fragmentation of the muscle fibers, accompanied by a breakdown of the chromatin of the nuclei.

The late changes in dystrophic muscle fibers are identical with those observed in the final stages of denervation atrophy.

In the case of progressive muscular dystrophy the nerve fibers in the nerve trunks remained intact, but degeneration of the muscle fibers apparently led to loss of contact at the myoneural junction, and this was followed by abortive regeneration of the terminal nerve fibers.

Thus, the appearance of advanced atrophy in the muscle fibers, intact large intramuscular nerve trunks and abortive terminal regeneration of the nerve fibers were characteristic features of muscles in a case of progressive muscular dystrophy.

In cases of the so-called secondary myopathies, such as peroneal muscular atrophy, the nerve trunks are empty or contain both normal fibers and empty Schwann tubes. They may, however, occasionally contain regenerated nerve fibers. This may indicate that some of the anterior horn cells have not undergone irreversible changes but are capable of sending out new axons.

Biopsy of muscle with study of the pattern of innervation may afford valuable aid to diagnosis in unusual cases of muscular atrophy and weakness.

Prof H J Seddon gave us permission to publish these cases.

Wingfield-Morris Orthopaedic Hospital

# EFFECTS OF *l*(+)-GLUTAMIC ACID AND OTHER AGENTS ON EXPERIMENTAL SEIZURES

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**C**LINICAL reports <sup>1</sup> of the efficacy of glutamic acid in the symptomatic therapy of patients with petit mal and psychomotor epilepsy prompted the following investigation of the effects of this amino acid on electrically and chemically produced convulsions in laboratory animals, in order to determine whether glutamic acid could be shown experimentally to be an anticonvulsant agent and to compare its efficacy and mechanism of action with other anticonvulsant drugs

## METHODS AND PROCEDURES

Mice, rats, cats, rabbits and monkeys were used in metrazol <sup>2</sup> experiments. Rats, cats, rabbits and monkeys were employed for a variety of electric shock experiments. The effect of glutamic acid was also investigated in rats in which the electric shock threshold had been previously lowered by hydration (produced by orally administered water or by experimental selective loss of extracellular electrolyte). Electric shock seizures were induced by an Offner 60 cycle alternating current apparatus. Spiegel corneal electrodes were employed. For direct cortical stimulation (rabbits) single condenser discharges were delivered through epidural electrodes. Electroencephalograms were recorded with a Ralim encephalograph, standard scalp electrodes were used with monkeys and epidural leads with rabbits.

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Financial assistance was received from the Committee on Therapeutic Research, Council on Pharmacy and Chemistry, American Medical Association, the Research Fund, University of Utah School of Medicine, and the Abbott Laboratories

1 (a) Price, J C, Waelsch, H, and Putnam, T J *dl*-Glutamic Acid Hydrochloride in Treatment of Petit Mal and Psychomotor Seizures, *J A M A* **122** 1153-1156 (Aug 21) 1943 (b) Waelsch, H, and Price, J C Biochemical Aspects of Glutamic Acid Therapy for Epilepsy, *Arch Neurol & Psychiat* **51** 393-396 (April) 1944

2 Supplied by the Bilhuber-Knoll Corporation

The natural *l*(+) isomer<sup>3</sup> of glutamic acid, rather than the racemic form, was employed in these experiments, inasmuch as Waelsch and Price<sup>1b</sup> suggested that the therapeutic effects could be ascribed to the former compound. It was given orally either in an acacia suspension or as a solution of the sodium salt. The latter was also employed for parenteral administration. The sodium salt was prepared by neutralization with sodium hydroxide to *p*<sub>H</sub> 7.0. Doses employed ranged from 0.25 to 6.0 Gm per kilogram of body weight calculated as the amino acid and were designed to cover and exceed, on a body weight basis, the range of doses reported to be effective clinically. When subcutaneous and intraperitoneal injections were made, the solution of sodium glutamate was injected in a concentration of 3 per cent (isomolar with body fluids) or 10 per cent. Because of the large volume of solution employed at the higher dose levels, control animals were given injections of a comparable volume of a solution of sodium chloride isomolar with the solution of sodium glutamate. In each type of experiment, in addition to controls, comparison was made of glutamic acid and one or more clinical or experimental anticonvulsants, such as phenobarbital, diphenylhydantoin, benzimidazole, Tridione (3,5,5-trimethyloxazolidine-2,4-dione)<sup>4</sup> and dimethyl-N-methyl barbituric acid.<sup>4</sup>

## RESULTS

### METRAZOL-INDUCED CONVULSIONS

*Mice and Rats*—Twenty albino mice were given the solution of sodium glutamate by mouth in doses of 0.5 or 1 Gm of the amino acid per kilogram of body weight. After from two to five hours, a standard convulsant dose of metrazol (*CD*<sub>95+</sub>), 85 mg per kilogram of body weight, was injected subcutaneously.<sup>5</sup> Ten control mice were given the solution of sodium chloride by mouth in comparable volume and similarly received injections of metrazol. Single doses of glutamic acid had no discernible effect on the metrazol-induced convulsions. Indexes employed for comparison in these, and in subsequent, experiments included time of onset, character and severity of the convulsion and period required for recovery. Tridione and dimethyl-N-methyl barbituric acid, in doses not significantly depressant, are completely protective against twice the convulsant dose of metrazol.<sup>6</sup> The efficacy of phenobarbital and

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3 The *l*(+) glutamic acid and diphenylhydantoin sodium were supplied by Dr. Oliver Kamm, of Parke, Davis & Company, Detroit.

4 These substances were supplied by Dr. R. K. Richards, of the Abbott Laboratories, North Chicago, Ill.

5 Goodman, L. S., and Lih, B. Effect of Dilantin on Metrazol Convulsions, *J. Pharmacol. & Exper. Therap.* **72**: 18, 1941. Lih, B. The Protective Action of Dilantin Against Metrazol Convulsions, Thesis, Yale University School of Medicine, New Haven, Conn., 1941.

6 (a) Goodman, L. S., and Manuel, C. The Anticonvulsant Properties of Dimethyl-N-Methyl Barbituric Acid and 3,5,5-Trimethyloxazolidine-2,4-Dione (Tridione), *Federation Proc.* **4**: 119-120, 1945. (b) Goodman, L. S., and Toman, J. E. P. Experimental Indices for Comparing the Efficacy of Compounds with Anticonvulsant and Antiepileptic Properties, *ibid.* **4**: 120, 1945. (c) Everett, G. M.,



other barbiturates is well known. Single large doses of diphenylhydantoin are not anticonvulsant in this category of experiments.<sup>5</sup>

Inasmuch as certain anticonvulsant agents may not be effective clinically until medication has been carried out for several days, chronic experiments were conducted. Twenty albino mice and 10 albino rats were given sodium glutamate solution by mouth twice daily for five days, the single dose being 0.5 or 1 Gm per kilogram of body weight. The standard convulsant dose of metrazol was then injected from two to five hours after the last dose of glutamic acid. For rats, this dose is 70 mg per kilogram of body weight (CD<sub>50</sub>)<sup>5</sup>. Control groups of 10 mice and 10 rats were intubated with comparable volumes of sodium chloride solution for five days and similarly tested with metrazol. Chronic treatment with glutamic acid did not modify the response to metrazol. Chronic therapy with diphenylhydantoin significantly reduced the incidence, severity and lethality of metrazol-induced convulsions in mice and rats tested as described here.<sup>5</sup>

*Rabbits*—Three rabbits were prepared with epidural electrodes for electroencephalographic recording from both motor and occipital areas. Sodium glutamate solution was injected intraperitoneally and subcutaneously in doses of 0.5, 1 and 2 Gm per kilogram of body weight, respectively, given twice daily for two days. From three to five hours after the first and the last injection electroencephalographic records were taken. Metrazol was then administered subcutaneously, 40 mg per kilogram, and electroencephalographic recordings were made periodically. After injection of glutamic acid and before the injection of metrazol, the electroencephalographic record revealed no significant change from normal.

The electroencephalographic and motor responses to metrazol were in no way modified by glutamic acid, as revealed by control injections of metrazol in the same 3 rabbits and by comparison with numerous other controls. In contrast, phenobarbital, Tridione, dimethyl-N-methyl barbituric acid and benzimidazole, but not diphenylhydantoin, afford complete protection against the electroencephalographic and motor effects of convulsant doses of metrazol in rabbits.<sup>7</sup> Prior to the metrazol seizure, electroencephalographic responses occur in rabbits which simulate inter-seizure petit mal records in human subjects. Despite the reported clinical efficacy of glutamic acid for petit mal and psychomotor seizures, no

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and Richards, R. K. Comparative Anticonvulsive Action of 3,5,5-Trimethyl-oxazolidine-2,4-Dione (Tridione), Dilantin and Phenobarbital, *J. Pharmacol. & Exper. Therap.* **81** 402-407, 1944, (d) Comparative Anticonvulsant and Hypnotic Action of Some Barbituric Acid Derivatives, *Federation Proc.* **4** 20, 1945.

<sup>7</sup> Goodman, L. S. The Pharmacodynamic Actions of Benzimidazole. A Preliminary Report, *Bull. New England M. Center* **5** 97-100, 1943. Goodman and Manuel<sup>6a</sup> Goodman and Toman<sup>6b</sup>

influence of the amino acid was detectable on the metrazol-induced petit mal type of dysrhythmia

*Cats*—Four cats were given glutamic acid intraperitoneally (0.25, 0.5, 1 and 4 Gm per kilogram of body weight, respectively) and one to three hours later intravenous injections of 10 mg of metrazol ( $CD_{50+}$ ) per kilogram of body weight. Glutamic acid neither protected against nor modified the metrazol seizure. In contrast, phenobarbital, Tridione, dimethyl-N-methyl barbituric acid and benzimidazole but not diphenylhydantoin) completely prevent metrazol convulsions.<sup>7a</sup>

*Monkeys*—In 3 monkeys (*Macaca mulatta*) control electroencephalograms and seizure responses to metrazol (50 to 90 mg per kilogram) administered subcutaneously were established. One week later a solution of sodium glutamate (0.5, 1 and 2 Gm, respectively per kilogram of body weight) was injected subcutaneously and intraperitoneally. Metrazol was then given two to four hours after the glutamic acid and failed to alter the preconvulsive ("petit mal") electroencephalogram, the seizure electroencephalogram or the convulsion itself. In contrast, phenobarbital, Tridione, dimethyl-N-methyl barbituric acid and benzimidazole afford complete protection against convulsant doses of metrazol, diphenylhydantoin, however, is not protective.<sup>7</sup>

#### ELECTRIC SHOCK EXPERIMENTS

*Rats*—Control thresholds averaged 28 milliamperes and varied from 24 to 36 milliamperes (0.2 second) in 10 rats. Sodium glutamate solution was injected subcutaneously in 3 groups of 2 rats each at dose levels of 0.25, 0.5 and 1 Gm, respectively, per kilogram of body weight. Two to five hours later the electric shock thresholds were found to be unaltered in all 10 rats. The 6 experimental rats were then given sodium glutamate for four days, the aforementioned single doses being repeated twice a day. The control rats were similarly treated with solution of sodium chloride. The electric shock thresholds were again determined within one to three hours after the last dose and were found unchanged. The character, severity and duration of the seizures were not modified. Phenobarbital, Tridione and benzimidazole are capable of elevating the electric shock seizure threshold, but diphenylhydantoin is capricious and inconstant in this respect, such elevations as have been observed being insignificant in degree.<sup>8</sup> Tridione was given in large doses (400 mg per kilogram, intraperitoneally) and sodium diphenylhydantoin both in single doses (50 to 100 mg per kilogram,

<sup>7a</sup> Everett and Richards<sup>6c,d</sup> Goodman and associates<sup>7</sup>

<sup>8</sup> (a) Footnote 7 (b) Merritt, H. H., and Putnam, T. J. A New Series of Anticonvulsant Drugs Tested by Experiments on Animals, *Arch Neurol & Psychiat* **39** 1003-1015 (May) 1938

intraperitoneally) and in repeated smaller doses (25 to 50 mg per kilogram, intraperitoneally twice daily for one week)

Two groups of 2 rats each were also tested with supramaximal currents (150 milliamperes, 0.2 second) one, two and five hours after receiving 3 and 6 Gm, respectively, of sodium glutamate per kilogram of body weight (divided equally between the oral subcutaneous and intraperitoneal routes). The resulting maximal seizures were unaltered in severity, character and duration by the amino acid treatment. Other anticonvulsants abolish the tonic phase of the maximal convulsion.<sup>9</sup>

*Cats*—A typical severe tonic-clonic seizure is produced in cats by supramaximal stimulation (300 milliamperes, 0.2 second). Single doses of glutamic acid given by mouth (0.5 to 1 Gm per kilogram) or parenterally (4 Gm per kilogram) did not alter the maximal seizures in 5 cats. Each cat had previously been tested with parenteral injections of phenobarbital (15 mg per kilogram), diphenylhydantoin (10 to 40 mg per kilogram), Tridione (400 mg per kilogram) and dimethyl-N-methyl barbituric acid (100 to 125 mg per kilogram), in every instance, the tonic phase of the seizure was completely obliterated. Furthermore, benzimidazole (350 mg per kilogram) completely abolished the convulsion. These experiments and their significance will be reported in detail elsewhere.<sup>9</sup>

*Rabbits*—Direct Cortical Stimulation. Epidural electrodes were implanted over symmetric areas of both hemispheres in 3 rabbits, to permit stimulation of the motor cortex on one side with single condenser shocks while the electrical activity of the opposite side is recorded. Thresholds were determined for primary and secondary electroencephalographic discharges<sup>10</sup> and for contralateral facial movements. Sodium glutamate in single doses of 1.5 Gm per kilogram given intraperitoneally failed to alter these three thresholds significantly when tested at intervals up to three hours after injection and failed also to alter the typical wave form of the secondary discharge. In contrast, sodium phenobarbital (20 mg per kilogram, intravenously) increased all three thresholds and altered the wave form of the secondary discharge. In minimally depressant doses, benzimidazole (100 mg per kilogram, given intravenously) was more effective, and Tridione (400 mg per kilogram, given intraperitoneally) less effective, than phenobarbital in raising thresholds. Diphenylhydantoin (60 mg per kilogram, given intraperitoneally) was ineffective.

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9 Toman, J. E. P., Swinyard, E. A., and Goodman, L. S. Characteristics of Maximal Electroshock Convulsions. Their Modification by Drugs and Other Experimental Procedures, *J. Neurophysiol.*, to be published.

10 Toman, J. E. P. Cortical Responses to Cortical Stimulation in Relation to the Spontaneous EEG of the Rabbit, *Federation Proc.* 4:72, 1945.

*Monkeys*—A single oral dose of 0.5 to 1 Gm per kilogram of sodium glutamate failed to alter the electric shock threshold in 4 monkeys (*Macaca mulatta*) or the duration or severity of the seizures. The control thresholds ranged from 34 to 52 milliamperes (5 seconds' stimulation). In all 4 monkeys the individual electric shock threshold remained constant within a variation of 10 per cent over a period of six months. Tridione and diphenylhydantoin in single large or in repeated small doses and dimethyl-N-methyl barbituric acid gave inconstant and capricious elevations in seizure thresholds (10 to 30 per cent). In contrast phenobarbital and benzimidazole consistently elevated the electric shock convulsive threshold.

*Hydrated Rats*—Rats hydrated by the oral administration of 4 doses of water at one-half hour intervals (5 cc per hundred grams of body weight per dose) manifested a reduction in electric shock threshold of 36 to 76 per cent (average 56 per cent, 51 rats). Three pairs of rats, whose response to hydration was known, received orally 0.5, 1 and 2 Gm per kilogram, respectively, of glutamic acid in acacia suspension. The electric shock threshold was retested thirty minutes after the last dose of water. The amino acid failed to protect against the lowering of threshold produced by hydration. In sharp contrast, phenobarbital, diphenylhydantoin, Tridione, dimethyl-N-methyl barbituric acid and benzimidazole all elevated considerably the electric shock threshold lowered by this type of hydration.

A second type of hydration of brain tissue was accomplished by the technique of Darrow and Yannet,<sup>11</sup> which involves the intraperitoneal injection of isomolar solution of dextrose (5.5 per cent, 10 cc per hundred grams of body weight) and its subsequent removal (250 to 280 minutes) after it has equilibrated with the extracellular fluid. The volume of fluid removed approximated that administered, so that total body water was not altered. By this means, nearly 40 per cent of extracellular electrolyte was lost to the body. Osmotic equilibration occurs through a shift of extracellular water into the cellular compartment. With employment of accepted values for distribution of body water and electrolyte, it can readily be calculated that cell volume may increase by 14 per cent. The "hydration threshold" (the electric shock threshold at the time of maximal cellular hydration) was reduced an average of 56 per cent (50 to 64 per cent, 24 rats). When glutamic acid in acacia suspension was administered to 4 rats in a dose of 0.5 or 1 Gm by mouth and the procedure repeated as previously outlined, no significant change occurred in the hydration threshold. Quite dif-

11 Darrow, D. C., and Yannet, H. Changes in Distribution of Body Water Accompanying Increase and Decrease in Extracellular Electrolyte, *J. Clin. Investigation* **14**: 266-275, 1935.

ferent results were obtained when diphenylhydantoin, phenobarbital and Tridione were administered parenterally at a time which would allow their peak effects to become manifest coincident with the maximal reduction in electric shock threshold produced by hydration. The marked increase in hydration threshold caused by these three anticonvulsant agents and the inefficacy of glutamic acid are shown in the accompanying table.

It is apparent from the results obtained with glutamic acid in rats with brain cells hydrated by orally administered water or by experimental selective loss of extracellular electrolyte that the amino acid not only is incapable of elevating the electric shock threshold of normal

*Inefficacy of Glutamic Acid in Lowering "Hydration Threshold" in Rats and Increase in Threshold Produced by Three Anticonvulsant Drugs*

Rat No	Rat Wt, Gm	Volume 5% Dextrose Injected Intraperitoneally, Cc	Time Between Injection and Parenthesis, Min	Volume of Fluid Removed, Cc	Concentration of Cation in Fluid Removed, mEq/L	Amount of Cation Removed per 100 Gm, mEq	Normal Electric Shock Threshold, Ma	Hydration Threshold After Parenthesis, Ma	Decrease from Normal Threshold, %	Threshold After Amino Acid or Drug, Ma *	Change from Hydration Threshold, %
1	300	30	255	29	126	1.22	30	14	53	G 12	- 14
2	284	28	260	27	126	1.20	36	14	61	G 16	+ 14
3	332	31	265	31	126	1.18	36	14	61	G 12	- 14
4	292	29	270	27	126	1.17	30	14	53	G 16	+ 14
5	316	32	250	32	126	1.28	30	12	60	D 18	+ 50
6	292	29	255	31	129	1.37	30	14	53	D 20	+ 43
7	288	29	265	28	135	1.31	26	10	62	T 20	+100
8	272	27	260	24	135	1.34	32	12	62	T 24	+100
9	340	34	280	33	135	1.31	24	10	58	P 18	+ 89
10	290	29	270	30	126	1.30	28	12	57	P 28	+133

\* G indicates glutamic acid given orally in 10 per cent acacia suspension. For rats 1 and 2 the dose was 0.5 Gm per kilogram of body weight, for rats 3 and 4, 1 Gm per kilogram. D indicates diphenylhydantoin sodium, given intraperitoneally in a dose of 50 mg per kilogram, T, Tridione, given intraperitoneally in a dose of 400 mg per kilogram, and P, phenobarbital sodium, given intraperitoneally in a dose of 45 mg per kilogram.

rats but is unable to protect against the lowering of threshold produced by hydration.

**Toxicity**—Unna and Howe<sup>12</sup> reported salivation, vomiting and bradycardia after intravenous injection of large doses of glutamic acid in unanesthetized dogs. Madden and others<sup>13</sup> attributed to glutamic acid the toxic effects of amino acid mixtures and protein digests given

12 Unna, K, and Howe, E. E. Toxic Effects of Glutamic and Aspartic Acid, *Federation Proc* 4: 138, 1945.

13 Madden, S. C., Woods, R. R., Shull, F. W., Remington, J. H., and Whipple, G. H. Tolerance to Amino Acid Mixtures and Casein Digests Given Intravenously. Glutamic Acid Responsible for Reactions, *J. Exper. Med* 81: 439-448, 1945.

intravenously To avoid these toxic effects, other routes of administration were used in our studies

In rabbits, glutamic acid given intraperitoneally in doses of 1.5 Gm per kilogram of body weight caused salivation, hyperpyrexia and impairment of placing reactions Unexplained death occurred within several hours in 1 of 3 rabbits receiving 1.5 Gm per kilogram and in both of 2 rabbits given 2 Gm per kilogram of body weight Even at this lethal level there was no evidence of anticonvulsant action of glutamic acid

Cats were found to tolerate 4 Gm per kilogram of body weight given intraperitoneally without toxic signs, but also without evidence of protection against metrazol or alteration in maximal electric shock seizures In 1 animal given 8 Gm per kilogram there developed salivation, hyperpnea and spontaneous tonic-clonic seizures, which increased in frequency and severity until death occurred, two hours after injection Rats tolerated up to 6 Gm per kilogram of body weight without toxic signs, but even at this high dose level there was no evidence of anticonvulsant activity The largest doses given to monkeys (2 Gm per kilogram of body weight) caused no alteration in temperature, respiration or neurologic signs

#### COMMENT

The experiments here reported provide no indication of the mechanism of action whereby glutamic acid may exhibit its reputed suppression of petit mal and psychomotor seizures<sup>1</sup> Although our laboratory indexes mainly concern major seizures, glutamic acid was also found ineffective against the petit mal type of electroencephalogram produced by subcutaneous injection of metrazol in rabbits and monkeys Other drugs known to be more or less effective clinically in management of petit mal give positive protection against this experimental type of petit mal dysrhythmia in laboratory animals

The two techniques which appear to us to be most useful as laboratory devices for testing potentially anticonvulsant drugs are the supramaximal electric shock method<sup>9</sup> and the cellular hydration method, as employed in this study, the latter has been reported on in full elsewhere<sup>14</sup> All clinically effective anticonvulsants except glutamic acid give positive results with these two techniques The cellular hydration method is of particular interest with regard to the question whether the electric shock seizure threshold is below normal in patients with epilepsy<sup>15</sup>

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14 Swinyard, E. A., Toman, J. E. P., and Goodman, L. S. The Effect of Cellular Hydration on Experimental Electroshock Convulsion, *J. Neurophysiol.* 9: 47-54, 1946

15 Garciadiego, J., Chavez, F. N., and Alcade, S. O. Aplicaciones del electro-choque como metodo de investigacion y diagnostico en los epilepticos, *Arch.*

Diphenylhydantoin, phenobarbital and Tridione are very effective in raising the threshold lowered by cellular hydration. Yet diphenylhydantoin is unable significantly to elevate the normal electric shock seizure threshold, this has been our consistent experience over a period of two years, employing rats, rabbits, cats and monkeys, and differs from the results of other investigators<sup>16</sup>. If it is true that known potent anticonvulsants in nondepressant doses cannot significantly elevate the normal electric shock threshold, then other laboratory methods of assay must be employed. The two suggested here seem most promising.

Since glutamic acid, even in large doses, showed neither anticonvulsant nor analeptic action with any of the methods employed, we are forced to conclude that its mechanism of action differs from that of all other clinical anticonvulsant agents. Investigations on the role of glutamic acid in cerebral metabolism and function<sup>17</sup> provide the basis for speculation on the possible nature of its action in epilepsy, but pertinent information is still lacking. One might postulate some subtle distortion of glutamic acid metabolism in patients suffering from petit mal. However, as Waelsch and Price<sup>18</sup> pointed out a daily protein intake of 70 Gm provides 7 to 10 Gm of natural glutamic acid, and the proteins of the body contain between 10 and 20 per cent of glutamic acid. By comparison, the doses of glutamic acid reported effective against petit mal (as little as 4.8 Gm per day) seem almost superfluous.

#### SUMMARY

In an attempt to measure in the laboratory the anticonvulsant value of glutamic acid, this substance was tested by a number of techniques

de neurol y psiquiat de Mexico **7** 117-128, 1944. Kalinowsky, L. B., and Kennedy, F. Observations in Electric Shock Therapy Applied to Problems of Epilepsy, *J Nerv & Ment Dis* **98** 56-67, 1943. Penfield, W., and Erickson, T. C. Epilepsy and Cerebral Localization, Springfield, Ill., Charles C Thomas, Publisher, 1941.

16 Merritt and Putnam<sup>16</sup> Knoefel, P. K., and Lehrmann, G. The Anticonvulsant Action of Diphenyl Hydantoin and Some Related Compounds, *J Pharmacol & Exper Therap* **76** 194-201, 1942. Tainter, M. L., Tainter, E. G., Lawrence, W. S., Neuru, E. N., Lackey, R. W., Luduena, F. P., Kirtland, H. B., Jr., and Gonzalez, R. I. Influence of Various Drugs on the Threshold for Electrical Convulsions, *J Pharmacol & Exper Therap* **79** 42-54, 1943. Everett and Richards<sup>16</sup>.

17 Krebs, H. A. The Synthesis of Glutamine from Glutamic Acid and Ammonia, and the Enzymic Hydrolysis of Glutamine in Animal Tissues, *Biochem J* **29** 1951-1969, 1935. Nachmansohn, D., John, H. M., and Waelsch, H. Effect of Glutamic Acid on the Formation of Acetylcholine, *J Biol Chem* **150** 485-486, 1943. Weil-Malherbe, H. Studies on Brain Metabolism. I. The Metabolism of Glutamic Acid in Brain, *Biochem J* **30** 665-676, 1936. Zimmerman, F. T., and Ross, S. Effect of Glutamic Acid and Other Amino Acids on Maze Learning in the White Rat, *Arch Neurol & Psychiat* **51** 446-451 (May) 1944.

for investigating the potency of anticonvulsant agents. In a wide range of single large and repeated small doses, and in a variety of species, the amino acid was found ineffective in the prevention or modification of electrically or chemically induced convulsions. Glutamic acid failed to elevate the normal seizure threshold, did not modify the character of the convulsion produced by supramaximal currents and had no effect on the electric shock threshold lowered by cellular hydration. Glutamic acid was also without effect on metrazol-induced electroencephalographic dysrhythmias of the petit mal type. In addition, it did not alter the resting electroencephalogram or the electroencephalographic response to single cortical shocks.

Inasmuch as diphenylhydantoin, phenobarbital, Tridione, dimethyl-N-methyl barbituric acid and benzimidazole give laboratory evidence of anticonvulsant potency with one or more of the technics employed, it is suggested that if further clinical work substantiates the efficacy of glutamic acid in treatment of petit mal and psychomotor epilepsy the mechanism of its action is likely to prove considerably different from that of the known anticonvulsant drugs in clinical use. Indeed, one would not be able to predict from present laboratory screening methods that glutamic acid has anticonvulsant potency or value.

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## SENSATION OF ELECTRIC SHOCK FOLLOWING HEAD INJURY

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RECENT observation of many cases of the sensation of electric shock on flexion of the neck as a result of war injuries has reawakened interest in this phenomenon, which was first noted and described during World War I. Heretofore it has been regarded as an interesting medical curiosity, chiefly because of its occurrence as a subjective symptom in cases of multiple sclerosis. Its appearance with this disease was described by Lhermitte, and the phenomenon is frequently referred to in the literature as "Lhermitte's sign." It is the purpose of this paper to report these recently observed cases, together with details of the variations of the symptom, for it is believed that this sign may be indicative of concomitant damage to the cord in cases of head injury and that it is of more than academic interest.

In an excellent brief review of the literature, Salmon<sup>1</sup> noted that in Babinski's neurologic service in World War I this phenomenon was observed in 12 cases, the data on these cases were abstracted by Ribeton<sup>2</sup> in his thesis published in 1919. Prior to this publication, however, Marie and Chatelin,<sup>3</sup> in 1917, reported a case of injury to the vertex and the occiput in which weakness of the arms was present, being more pronounced in the morning than in the evening, and in which flexion of the neck on the chest produced the sensation of an electric current running down both arms and legs. They noted that passive elongation of the brachial plexus gave the same response. Digital compression of the plexus caused pain in the shoulders and arms but did not produce the sensation of electric shock. They expressed the opinion that the cause of the phenomenon was an injury of the cervical

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Capt John A. Di Fiore and Capt Glenn S. Plaver, of the Medical Corps, Army of the United States, assisted in the collection of the material on which this paper is based.

1 Salmon, L. A. Sensation of Electric Shock in Multiple Sclerosis, *Bull Neurol Inst New York* 6: 378, 1937.

2 Ribeton, J. Étude clinique des douleurs à forme de décharge électrique consécutives aux traumatismes de la nuque, Thesis, Paris, no 134, 1919.

3 Marie, P., and Chatelin, C. Sur certains symptômes d'origine vraisemblablement radiculaire chez les blessés du crâne, *Rev neurol* 24: 336, 1917.

roots by contrecoup. The next year Babinski and Dubois<sup>4</sup> reported the case of an officer with an injury of the neck who had the sensation of electrical discharge on the right side only. This officer showed a Brown-Séquard syndrome with right hemiparesis. Every time he flexed his neck he had an electrical discharge the length of his right arm and leg. The authors also mentioned 3 other cases of injury to the neck without signs of any damage to the cord in which the phenomenon occurred bilaterally. In commenting on these cases, Lhermitte expressed the opinion that the phenomenon was due to "cervical irritation." In 1918 Beriel and Devic<sup>5</sup> reported a case in which the sensation of electric shock was associated with multiple sclerosis. In 1924 Lhermitte, Bollack and Nicolas<sup>6</sup> described the sign as occurring early in the course of multiple sclerosis. This was followed by a second paper by Lhermitte and other collaborators,<sup>7</sup> with an excellent clinical description of the sensation by the patient herself. It was described as being like the recurrent ringing of a telephone bell, with electrical discharge lasting for three seconds on flexion of the neck and disappearing for four seconds. The discharge in this patient occurred not only on flexing her neck but on raising her head from flexion. It was never present during complete rest. For this reason, Lhermitte concluded that fatigue was a factor in the occurrence of the sign. He explained the phenomenon on the basis of early demyelination.

Since that time many cases of the phenomenon have been reported or discussed as a sign of multiple sclerosis (Roger, Reboul-Lachaux and Aymes<sup>8</sup>, Triumphoff<sup>9</sup>, Wechsler<sup>10</sup>, Lhermitte<sup>11</sup>, Patrick<sup>12</sup>, Opalski,<sup>13</sup> and Read<sup>14</sup>

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4 Babinski, J, and Dubois, R. Douleur à forme de décharge électrique, consécutives aux traumatismes de la nuque, *Presse med* **26** 64 (Feb 4) 1918

5 Beriel and Devic, E. Sur un cas de douleurs a type de décharge dans la sclérose en plaques, *Lyon méd* **141** 559, 1918

6 Lhermitte, J, Bollack, and Nicolas, M. Les douleurs à type de charge électrique consecutives a la flexion céphalique dans la sclérose en plaques, *Rev neurol* **31** 56, 1924

7 Lhermitte, J, Levy, G, and Nicolas, M. Les sensations de décharge électrique symptôme précoce de la sclérose en plaques, *Presse méd* **35** 610, 1927

8 Roger, H, Reboul-Lachaux, J, and Aymes, G. Dysesthesies rachidiennes a type de décharge électrique par flexion de la tête dans la sclérose en plaques, *Rev neurol* **1** 1052-1055 (May 31) 1927

9 Triumphoff, A. A propos du symptôme de décharge électrique de la sclérose en plaques, *Presse méd* **35** 948, 1927

10 Wechsler, I S. A Case of Multiple Sclerosis with an Unusual Symptom, *Arch Neurol & Psychiat* **19** 364 (Feb) 1928

11 Lhermitte, J. Multiple Sclerosis. The Sensation of an Electrical Discharge as an Early Symptom, *Arch Neurol & Psychiat* **22** 5 (July) 1929

*Data on Thirty Patients Experiencing Sensation of Electric Shock as Result of Head Injury*

Patient No	Location of Injury, Size	Onset of Symptom After Injury	Duration of Symptom	Distribution of Sensation	Other Symptoms	Comment
1	Left temporal defect, 4 by 4 cm	4 wk	3 mo	Left side of neck and left arm	Transient weakness of left arm	Sensation disappeared before insertion of tantalum plate
2	Left frontoparietal defect, 1 by 4 cm	4 wk, immediately after clearing up of weakness of arms	5 mo	Spine and both arms	Weakness of both arms for month after injury	Epidural hemorrhage found at operation, plate inserted 4 weeks after injury
3	Left temporal defect, 3 by 2.5 cm	8 wk	3 mo	Chest, arms and thighs	Transient numbness of fifth fingers of both hands for 3 days after injury	No loss of consciousness
4	Linear fracture, right temporal region	7 wk	2 mo +*	Neck, anterior and posterior thoracic walls to D 4, both arms, D 6	None	Unconscious for 10 days, homonymous diplopia on looking to right, and vertigo
5	Left temporoparietal defect, 4 by 4 cm	11 wk	7 wk	Arms, posterior and anterior thoracic walls	Mild weakness of left arm still present	Electric sensation disappeared immediately after insertion of tantalum plate
6	Left parietal defect, 4 by 4 cm	15 wk	5 wk	Left side of neck, left arm and fingers	Transient numbness in distribution of left ulnar nerve	
7	Left temporal defect, 5 by 1.5 cm	9 wk	2 mo +*	Left anterior chest wall, left arm, left third, fourth and fifth fingers of left hand	Objects in left hand dropped on flexion of neck	Sensation not momentary but lasting 13 seconds
8	Left postauricular region, no fracture	3 wk	5 mo +*	Spine, arms and legs	Initial transient paralysis of both arms now weakness of both arms increased by flexion of neck	Shock on jugular compression momentary weakness of hands and sensory diminution on flexion of neck
9	Right occipital defect, 4 by 4 cm	3 wk	2½ mo	Inner tips of both hands	None	Residual left homonymous hemianopsia, deafness, and thinitis on right
10	Left temporal defect, 2.5 cm, dura not lacerated	2 mo	6 mo	Spine, both arms and hands	None	Sensation not momentary but may last 23 minutes if neck is kept flexed
11	Right frontal defect, 3 by 5 cm	13 wk	1 mo	Spine and legs	None	Sensation lasts 23 seconds
12	Left occipital defect, 4 by 5 cm	10 days	5 mo	Both hands	None	Electric shock lasts 2 minutes, recovery from right homonymous hemianopsia
13	Defect in left frontal lobe, 3 by 3 cm, fragment in left occipital lobe, 0.5 by 0.3 cm	3 mo	2 mo	Left arm and fingers, 2 weeks afterward right arm and fingers	None	After disappearance of shock on flexion of neck, sensation of electric shower in left finger tips on washing hands with water
14	Left parietal defect, 7 by 7 cm	1 mo	7 wk	Anterior wall of chest, abdomen, legs	None	Sensation not momentary but lasts 3 seconds worse at night

15	Loss of left eye, simple fracture of right parietal bone	2 mo	1 mo	Left arm, sternum to umbilicus	None	Shock not consistent, jugular compression diminished intensity of shock
16	Right frontal defect, 4 by 4 cm	6 mo	6 mo	Sensation felt deep in abdomen at level of umbilicus	None	No recurrence of electric shock since disappearance, 7 months ago
17	Left frontoparietal defect	1 wk	13 mo +*	Both arms, anterior wall of chest and epigastrium	None	Shock extremely weak and inconstant now but not completely gone
18	Right occipital defect, 4 by 2.5 cm	3 mo	8 wk	Ascending from neck to posterior portion of scalp	Left homonymous hemianopsia, tinnitus	
19	Left temporal and left occipital defects, each 4 by 4 cm	2 mo	Disappearance from legs in 2 mo and suddenly from rest of body in 3 mo	Both arms, trunk and legs, continuous on flexion of neck, persists for hours, not painful	Memory defect	Meningitis present, 11,020 cells per cu mm, 86 per cent polymorphonuclear cells, no organisms, treatment with sulfathiazole and intrathecal administration of penicillin
20	Right parietal defect, 6 by 6 cm	3 mo	3 mo	Only down spine	Left hemiparesis, transient numbness of right hand and foot, left hemianopsia, position and vibration senses impaired in left fingers and toes	Shock sensation lasts 2 seconds, all neurologic signs cleared up except slight weakness of left leg
21	Anterior left frontal defect, 2.5 by 3 cm, posterior left frontal defect, 1.5 by 2 cm	3 mo	1 mo +*	Neck, shoulders and spine but not arms	None	Complete retrograde amnesia for 12 weeks, recovery
22	Right occipital injury, no fracture	3 mo	2 wk *	Anterior wall of chest and both arms	None	Injury to left ulnar nerve 12 years ago, electric shock sensation does not radiate in distribution of left ulnar nerve
23	Simple fracture of left occiput	3 mo	1 mo *	Starts at spinous process of D8 vertebra, ascends to both shoulders and goes down both arms	None	Electric shock sensation produced only by flexion of trunk
24	Right temporal craniotomy, removal of meningeal fibroblastoma	5 mo	2 wk	Left side of forehead, face and neck, left arm and left leg	Left hemiplegia and hemianopsia, improved after removal of tumor	Sensation accidentally discovered on shaking of head, flexion did not produce sensation
25	Left frontoparietal defect, 3 by 3 cm	6 mo	1 wk	Both arms	None	Sensation stimulated by tapping dorsum of right great toe
26	Left parietal defect, 6 by 1 cm	11 mo after injury and 1 wk after recurrence of aphasia	1 wk	Ascends from right great toe up right side of body to face	Right spastic hemiparesis and hemihypalgnesia	
27	Left temporoparietal defect, 6 by 6 cm	2 mo	1 mo *	Left hand and fingers, mostly palmar	Patient recovering from right hemiplegia and aphasia	Arm most involved in paralysis
28	Bifrontal and left temporal defects	2 mo	1 mo *	Lateral aspect of right forearm and right fifth finger	Patient recovering from right hemiplegia	
29	Left frontoparietal defect	2 mo	1 mo	Entire right side of body from face down	Right hemiparesis and hemihypalgnesia, recovery	Sensation stimulated by jugular compression and bending of trunk
30	Left frontoparietal defect, 1 by 8 cm	6 wk	2 mo	Right arm from deltoid surface to palm, mostly along medial surface	Recovery from right hemiplegia	Sensation disappeared immediately after cranioplasty

\* Sensation of electric shock still present at time of writing

Patrick mentioned that the phenomenon has also been observed in cases of tumor of the spinal cord and of tuberculosis of the cervical vertebrae. In 1933 Olkon<sup>15</sup> and Hassin<sup>16</sup> each described the sign in a case of subacute combined degeneration of the cord. Hassin's case had the advantage of being studied pathologically, and the typical, well known characteristics of that pathologic entity were found. This author took issue with Lhermitte as to the explanation of the phenomenon and stated that he doubted whether early demyelination is the answer, since demyelination occurs late and the sign usually appears early in the disease. He expressed the opinion that the sign might be due to swelling of the spinal nerve fibers. He stated:

Additional factors are probably at play, either special sets of nerve fibers are affected or the destructive process is especially severe.

Neither process can be proved pathologically. In his review of the literature and in his paper reporting 6 cases, Salmon<sup>1</sup> stated the opinion that the sign may be as late as well as an early one in multiple sclerosis.

During World War II attention was first called to this sign in a paper recently published by Triumfov,<sup>17</sup> who was the author of a paper previously mentioned.<sup>9</sup> In a report of 23 cases of injury to the brain he stated that the intensity of the symptom is related to the nearness of the wound to the foramen magnum and that the sensation is usually more intense in the extremities on the side of the injury. In most of the cases the histories suggested to Triumfov that meningeal irritation probably on the basis of hemorrhage into the meninges and roots, was the cause. It was usual for the symptoms to develop at the time of healing of the wound or two or three weeks later. He assumed the formation of scar tissue and adhesions in the meninges. The symptom developed and disappeared gradually. Its usual duration in his series was one to two months.

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12 Patrick, H. T. The Symptom of Lhermitte in Multiple Sclerosis, *Arch Neurol & Psychiat* **23** 1075 (May) 1930.

13 Opalski, A. Acces paralytique (decharge paralytique) dans un cas de sclerose en plaque, *Rev neurol* **38** 281, 1931.

14 Read, C. F. Multiple Sclerosis with Lhermitte's Sign, *Arch Neurol & Psychiat* **27** 227 (Jan) 1932.

15 Olkon, E. M. Subacute Combined Degeneration with Symptom of Lhermitte in "Pernicious Anemia" Case, *J Nerv & Ment Dis* **77** 256, 1933.

16 Hassin, G. B. Paraplegia in Flexion and the Symptom of Lhermitte, *Arch Neurol & Psychiat* **29** 855 (April) 1933.

17 Triumfov, A. V. The Symptom of "Electrical Discharge" in Brain Injuries, *Am Rev Soviet Med* **2** 350, 1945.

## ANALYSIS OF CASES

The table presents an outline of the data on 30 patients recently observed in an Army general hospital, all of whom had suffered head injuries. The subjects ranged in age from 19 to 38 years. Some were not unconscious at all after their injury. The longest period of unconsciousness was ten days. Some of the patients had no neurologic sequelae, others had severe hemiplegia, from which recovery took place slowly. Twenty-five of the patients had comminuted fractures, with resultant defects in the skull of sizes indicated in the table. Three of the patients showed only simple linear fractures, and 2 had no roentgenographic evidence of skull fracture. The sites of the bony injuries and damage to the brain in these patients were as follows: frontal, 4, frontoparietal, 5, temporal, 6, temporo-parietal, 2, parietal, 5, and occipital, 4. Two patients had double defects—1, temporal and occipital, and the other, bifrontal and temporal. Twenty of the fractures occurred on the left side. A review of the cases indicates that the site of the lesion is probably not a factor in the production of the symptom.

The appearance of the phenomenon of electrical discharge varied from a few days to six months after the injury, the average time being nine weeks. At the time of this writing some of the patients are still experiencing the phenomenon. In most, however, the symptom has disappeared. The average duration for the patients in whom the sensation no longer exists was a little over three months.

All patients who did not describe an unequivocal sensation of electrical discharge were not considered. Patients who described tingling, numbness and tingling, or vibration were rejected for inclusion in this series. It was surprising that in many instances the patients spontaneously described this symptom, and in several it was the chief complaint, since it kept them from being comfortable; 1 patient was awakened from sleep at night because of the pain involved. Except in the cases to be mentioned specifically later, the description was a classic one. On flexion of the neck there was a momentary sensation of electric shock, which started in the neck and passed down the arms, spine and legs. Variations were numerous, in some patients the phenomenon was one sided, although bilaterality was more frequent. In most patients the electric shock was an invariable sequel to flexion of the neck. In the others it occurred only occasionally on flexion. In all patients the onset of the symptom was sudden. In a few its disappearance was sudden. For the most part, however, the disappearance was gradual. This brief summary indicates already some differences in the symptomatology in this series from that in *Triumfov's*. Except when indicated in the separate case reports, roentgenograms of the cervical portion of the spine and studies of the spinal fluid showed a normal condition.

GROUP 1—Analysis of the case material reveals no clearcut evidence that the single factor of concussion of the cervical portion of the cord is the chief determinant in production of the sign. However, for 7 of the patients (1, 2, 3, 5, 6, 7 and 8) the weight of the evidence certainly tends to confirm the original impression of Babinski and Dubois<sup>4</sup> that the phenomenon is due to damage to the cervical part of the cord by contrecoup. This evidence was deduced from the cases in which signs of damage to the cervical portion of the cord immediately followed the injury. Patient 1, for instance, had transient weakness in the left arm after an injury to the left temporal area, and he later experienced the phenomenon only in the left side of the neck and the left arm. Patient 2 suffered weakness of both arms for a month after an injury to the left frontoparietal area, and the discharge of electrical phenomenon appeared in his spine and in both

arms as his weakness began to clear up. Patient 3 had transient numbness of the fifth finger of both hands for three days after his head injury. The sensation of electrical discharge appeared eight weeks after his injury and lasted for three months in his chest, arms and thighs. Patient 6 had transient sensory loss in the distribution of the left ulnar nerve, and fifteen weeks after his injury a sensation of electric shock developed in the left side of his neck, in his left arm and in the fingers of his left hand.

As can already be noted, signs of both sensory and motor involvement referable to the cervical portion of the cord were in evidence in these patients. Careful study showed that this weakness was of the type referable to the cervical portion of the cord rather than due to involvement of the cerebral cortex. Patient 7 had excellent motor power in the left hand after a defect in the left temporal area of the skull and involvement of the left temporal lobe, from which he had recovered. Nine weeks after the injury the sensation of electric shock developed in the left anterior portion of the chest, the left arm and the third, fourth and fifth fingers of the left hand. If while holding something in his left hand he flexed his neck, the object would drop from his hand because of the sudden, but momentary, weakness.

Patient 8 showed the most extensive involvement of the cord. This soldier was struck in the left postauricular region by a swinging steel hook. He immediately fell unconscious. When he regained consciousness, within an hour, he had complete paralysis of both arms. An hour later he was able to move his arms, but the weakness persisted. Gradually it cleared up so that his power was about 80 per cent normal. Sensory examination showed definite diminution of all modalities of sensation from the fourth to the eighth cervical segment. Three weeks after the head injury he began to notice a sensation of electric shock which passed down both arms, the spine and both legs. On flexion of the neck, there was an increase in the weakness in his hands, and he occasionally dropped objects which he was holding. Also, he reported that momentarily, for the duration of the shock, which was not particularly disconcerting, there was an increase in numbness. This could be tested and was best discernible with vibratory sense. He was the only patient studied in this series in whom the sensation of electric shock could be initiated by jugular compression, with this procedure he received the same momentary sensation of shock. It is, perhaps, worth while to note that roentgenologic studies showed no evidence of fracture of the spine or the skull. Studies of the spinal fluid revealed a normal condition. Since all these patients received their injuries in combat and immediate surgical intervention was available for them, there was no particular indication for studies of the spinal fluid, hence there are no reports on such studies done at the time of the injury. Examinations of the spinal fluid which are reported on here are those made at the time of study, usually months after the injury. In case 8, however, an examination of the spinal fluid was done immediately after the injury, and there was no evidence of any abnormality.

GROUP 2—According to the opinions expressed by various authors, the patients in the first group all presented a condition in which there is neurologic evidence of injury to the cord concomitant with the head trauma. In the next group to be considered (patients 4, 9, 10, 12, 13, 19, 22, 25 and 27) symptoms not unlike those of the first group were presented, but there was no direct evidence of sensory or motor changes in the upper extremities. On the basis of similarity of the nature and distribution of the sensation of electric shock, it is likely that the etiologic factor is the same. Yet it must be noted that variations in the dis-

tribution were more evident. In patient 4, for instance, the sensation of electric discharge had a segmental distribution from the second cervical to the fourth dorsal segment, and along the sixth dorsal segment, skipping the fifth dorsal segment.

Patient 9 experienced the phenomenon only in the finger tips. In patient 10, previously mentioned, in whom the sensations were so intense as to cause awakening from sleep, the phenomenon was not momentary but would last as long as three minutes. Also, for reasons unknown, there were periods of two or three days in which the phenomenon could not be elicited at all by any means. It would then reappear and last for two or three days. The patient, "a health addict," found that after a series of Turkish baths the sign disappeared entirely for ten days. On discontinuation of the baths the attacks resumed their usual frequency and intensity, to diminish gradually as time went on.

How complex and variable the phenomenon may be is illustrated by case 13. The soldier was struck by a shell fragment in the left frontal region, after débridement, a defect measuring 3 by 3 cm. was left in that region. Roentgenographic examination showed a small fragment lodged in the left side of the occiput. This soldier had right hemiplegia, aphasia and right homonymous hemianopsia. At the time of this writing he has recovered completely from his aphasia, his hemiplegia has almost entirely disappeared and only the hemianopsia remains. Three months after his head injury, on flexion of the neck, the sensation of electric shock appeared in his left arm and the fingers of his left hand. Two weeks later the phenomenon appeared in the right arm and fingers and was then bilateral. Two months after its appearance the sensations on flexion of the neck began to disappear and within a few weeks were completely gone. The phenomenon disappeared from the right side more quickly than it did from the left. During this period of subsidence the patient noted that if his left hand came in contact with water sensations of electric shock occurred in the finger tips of the left hand, but after a week they also disappeared. After this, however, he noted that if he rubbed his face with his left hand when he was bearded and needed a shave, tingling would appear in the finger tips. The phenomenon could be elicited only over the bearded portion of the face, and only in the left hand. The last-mentioned subjective symptom of tingling was not the same as the phenomenon of electric shock. This soldier showed roentgenographic evidence of lipping of the anterior margin of the sixth cervical vertebra, which was interpreted as evidence of mild arthritis and as having nothing to do with the phenomenon under discussion.

In another unusual case, that of patient 19, details of the nature of the injury are not clear, but it seems from the medical records available that the soldier suffered a bullet wound the point of entrance of which was the left temporal region and the point of exit the left occipital region. In both these areas he had defects in the skull measuring 4 by 4 cm. On arrival at this hospital, two months after his injury, he had pronounced amnesic aphasia and he had no memory whatever for events prior to his injury. Since then he has gradually recovered much of his pretraumatic history. On his admission, it was noted that there was slight bulging of both cranial defects and that he had a low grade fever. Spinal tap revealed the presence of 11,000 cells per cubic millimeter, with 86 per cent polymorphonuclear cells. On treatment with sulfathiazole and intrathecal administration of penicillin the cell count dropped to about 450 per cubic millimeter, all of which were lymphocytes. The spinal fluid pressure was very low. At the time of writing, he still has occasional low grade fever. Organisms have never



been cultured from the spinal fluid. The cause of the patient's meningitis remains a diagnostic problem, and various explanations have been offered, including that of sterile abscess. He is free of complaints.

After the initiation of the antimeningitis therapy, the patient became aware of sensations of electric shock on flexion of his neck. They occurred in both arms and ran down the entire body and both legs. The sensation of shock continued as long as the neck was kept flexed and disappeared only when it was extended to a normal position. The sensation was not painful. After two months the sensation of electric shock on flexion of the neck began gradually to disappear in his legs, and after three months it disappeared from the entire body.

It is clear that in the two large groups delineated here nerve pathways mediate the electric discharge. Additional confirmation is gathered from case 23. The soldier had had an accident in civilian life, resulting in partial palsy of the left ulnar nerve. After his head injury and the development of the phenomenon of electric discharge he experienced the sensation down both arms but not along the sensory distribution of the left ulnar nerve.

GROUP 3—Seven of the cases (11, 14, 15, 16, 17, 20, and 21) are placed together because it is difficult to explain the distribution of the electric discharge via anatomic nerve pathways. The radiation down the spine and legs in patient 11 can be explained anatomically, but the more common radiation down the arms was absent. Patient 14 had, besides his cranial injury, minute metallic bodies just above and posterior to the spinous process of the sixth cervical vertebra, surprisingly, the electric discharge did not radiate down his arms but only down the anterior thoracic wall, the abdomen and both legs.

Patient 15, for instance, felt the shock in his left arm and fingers, but it also traveled down the sternum and anterior abdominal wall in a narrow strip to the level of the umbilicus. Patient 15, curiously, felt the sensation of shock deep within the abdomen at the level of the umbilicus, and at no time did he have the sensation anywhere else. The longest duration of the sensation in any patient of this series was that in patient 17, who still experiences the phenomenon, though definitely diminished in intensity, after thirteen months. Interestingly, the period after injury at which his sensations began was the shortest in the series. Patients 20 and 21 also had unusual distributions of the electric discharge, the one only down the spine and the other down the neck, shoulders and spine.

GROUP 4—The usual course of the electric discharge was downward. In 3 patients this direction was reversed. In patient 18 the discharge began in the posterior part of the neck and ascended, to be felt in the posterior half of the scalp, the area involved was fairly congruent with the distribution of the second cervical spinal nerve. An unusual course of the discharge occurred in patient 23, in whom the sensation began at the spinous process of the eighth dorsal vertebra, ascended to the neck and then descended down both shoulders and arms.

Patient 26 was struck by numerous shell fragments in the left parietal region, and several fragments could not be removed at operation. Sequelae to his injury were right spastic hemiplegia, expressive aphasia and a right hemisensory syndrome. Eleven months after his injury the aphasia and sensory changes had disappeared and the hemiplegia had improved to the point at which he could walk with the aid of a cane. One night he indulged heavily in alcoholic beverages. He experienced a sudden headache, his motor aphasia recurred, and the hemiplegia became severe, so that he became bedridden. Jacksonian twittings of the right side of the face appeared. Examination of the spinal fluid showed nothing abnormal. Two days later his aphasia began to clear, and he complained of strangeness of feeling on the right side of the body, especially in the hand. The

right arm and hand often felt as though they did not belong to him. Pain, touch and temperature senses were impaired on the right side. Position sense was absent from the right hand but not from the toes. This exacerbation lasted a week and then recovery was rapid. During the week of sensory disturbance it was discovered that tapping the ball of the right great toe with a reflex hammer initiated sharp electric shock which ascended from the toe up the foot, leg and thigh, the right side of the abdomen and chest and the right shoulder, down the right arm and up the right side of the neck. The face was not involved. The electric sensation could not be elicited by any other means.

GROUP 5—Though the clinical picture presented by patient 26, just described, does not fit into the usual pattern of the phenomenon under discussion, it provokes interest in the possibility of cerebral involvement as a major etiologic factor in some cases. The cases of 4 other patients appear, from their clinical course, to constitute a group in which this may be true.

Patient 24, a 24 year old soldier, suffered from headaches and gradually diminishing vision. At operation a meningeal fibroblastoma filling the entire right middle fossa was successfully removed. After the operation he had left hemiplegia and hemianopsia, but his condition gradually improved. Five months after the right temporal craniotomy he noted sensations of electric shock on flexion of the trunk. The sensation of shock began in the left side of the forehead, descended down the left side of the face and neck and the left arm and leg, skipping the thorax and abdomen. The symptom persisted two weeks.

The case of patient 26 was described in the preceding group. The electric discharge was present only during the acute encephalopathic episode and then disappeared, thus being suggestive of an intimate causal relationship.

Patient 28 suffered a bifrontal and left temporal injury, with right hemiplegia, involving chiefly the arm. Two months after his injury there developed the sensation of electric discharge down the right arm and forearm and the fifth finger.

Patient 29 suffered right hemiparesis and hemihypalgesia, from which he recovered. During the period of recovery and for two months after his injury, on bending the trunk he experienced the phenomenon of electric shock down the entire right side of his body, beginning with the face. The sensation could also be elicited on jugular compression.

Patient 30, likewise, while recovering from right hemiplegia, experienced the sensation of electric discharge down the right arm. The phenomenon disappeared immediately after cranioplasty and the insertion of a tantalum plate.

An additional case, not listed in the table, exemplifies another variation of the phenomenon which appears best explained on the basis of a cerebral factor. The 21 year old soldier was struck by a mortar shell fragment in the left frontoparietal region. He was not unconscious and never had any complaints. At operation the dura and brain were found to be lacerated, but only slightly. Ten weeks after the injury he had a cranioplasty, and a tantalum plate was inserted over the defect. One month later, while lying in bed, he experienced a sudden, severe shock at the site of the injury. The sensation of shock spread rapidly over the entire body and lasted about two seconds. It was experienced most strongly in the posterior part of the neck, where it was painful. Three nights later and one week later identical attacks took place. There have been no similar episodes since. The soldier said that the shock was as though a live electric wire were placed on his head at the site of the injury and operation and the electric current ran through his entire body. No motor phenomena accompanied the sensations.

## COMMENT

The clearest discussion of the possible explanation of the phenomenon is that given in a review of the subject by Lhermitte<sup>18</sup>. He stated that since the phenomenon can be caused by passive flexion of the neck without contraction of muscles or effort, and since it occurs with multiple sclerosis, subacute combined disease of the cord and injuries of the cord, the most likely explanation lies in the pathologic process common to all these conditions, namely, recent demyelination. The sensation of shock is not unlike that experienced by patients with peripheral nerve injuries, known as Tinel's sign. Therefore Lhermitte mentioned this phenomenon as an analogous situation in which a similar pathologic condition exists. When one considers how forceful a trauma some of these soldiers have sustained, as in the case in which a missile entered the left temporal region and made its exit from the left occipital region, it is not at all surprising that the same force could have damaged the cord. This concomitant injury of the cervical portion of the spine and of the cord in association with head injuries has of course been noted before in the literature. It was recently emphasized by Walshe<sup>19</sup>. In the present series all cases in group 1 and most of the cases in group 2, are suggestive of concomitant concussion of the cord. Many cases of group 3 and cases 18 and 23, of group 4, may also fall into this category.

To the various discussions on the pathophysiology of the condition this series of cases, unfortunately, does not add much except to stress that whether or not the process is one of demyelination it is definitely reversible. The overwhelming number of cases of open head injuries (in this series, 25 with defects of the skull and only 5 with closed injuries) cannot be without significance. Since undoubtedly bleeding is present in the open wound, some weight is thrown toward support of Trumfov's hypothesis that a causative factor may be meningeal adhesions around nerve roots following bleeding. Yet in only a few cases in group 1 were there signs of radiculopathy, and there was in no instance any clinical picture resembling adhesive arachnoiditis.

In consideration of the possibility of meningeal adhesions another hypothesis presents itself. Could the presence of adhesions at the site of the defect, where in most instances there was laceration of the brain and dura, fixate the brain, so that flexion of the neck caused an extension of the cervical portion of the cord and irritation of the

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18 Lhermitte, J. Le signe de la decharge electrique dans les maladies de la moelle epiniere. Le signification semiologique, *Gaz d hop* **106** 1017, 1933.

19 Walshe, F. M. R. Note on a Commonly Unrecognized Type of Injury to the Cervical Spine and Spinal Cord in Association with Head Injuries, *Lancet* **2** 173, 1944.

cervical roots? Nothing conclusive can be deduced from this series in answer to this question except that in 2 cases (6 and 30) the sign disappeared immediately after cranioplasty

The cases in group 5 argue for an overwhelming cerebral factor in the production of the phenomenon. Whether one should go so far as to postulate a separate cerebral center for perception of electrical sensation is doubtful. Yet such a hypothesis might be ventured, since both perceptual and inhibitory centers for qualitative sensations related to the phenomenon of electric discharge are being discovered.<sup>20</sup> Whether in this connection the large number of left-sided lesions (in two thirds of the cases) is a factor is conjectural. Nor is the fact that in several cases the phenomenon could be produced by bilateral jugular compression or by bending of the trunk considered evidence for or against either the hypothesis of a cerebral origin or that of concussion of the cord.

Attempts to correlate the symptoms with the site of the lesion, the duration of unconsciousness and the nature and time of operative intervention have failed. Triumfov's observations that the symptom is usually experienced on the same side of the body as the head injury and that an injury in the parasagittal region leads to bilateral perception of the symptom are not corroborated by the evidence in this larger group of cases.

Since Lhermitte stated in several papers that in his opinion the phenomenon may be due to actual generation of electricity, studies with the neurodermometer were made in a series of these cases. In no instance could a change in electrical resistance of the skin be detected with this instrument during the phenomenon. Use of the electroencephalogram, in an attempt to pick up "electrical currents" with electrodes along the course of the "discharge," failed to produce any deviation during the production of the sensation.

#### SUMMARY

A series of 30 cases of head injury is presented in which the phenomenon of sensation of electric shock was perceived in various parts of the body on flexion of the neck. Multiple etiologic factors may be operative, the hypothesis of concomitant concussion of the cord and of a special cerebral origin are discussed. The pathologic process is unknown, demyelination of spinal tracts and meningeal scars being considered as likely factors, the process, however, is self-limited and reversible so far as the phenomenon is concerned.

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<sup>20</sup> Yacorzynski, G. K., and Davis, L. Studies of the Sensation of Vibration. *Arch Neurol & Psychiat* 53:355 (May) 1945.

## NEUROPSYCHIATRIC OBSERVATIONS ON TSUTSUGAMUSHI FEVER (SCRUB TYPHUS)

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ALTHOUGH records indicate that tsutsugamushi fever (scrub typhus, Japanese river fever, kedani fever, Japanese flood fever) has been known to exist for over a thousand years, the American medical profession had little experience with the disease until it was encountered among troops stationed in certain areas of the Southwest Pacific theater of the war. Tsutsugamushi, which is caused by *Rickettsia nipponica* (*Rickettsia orientalis*, *Rickettsia tsutsugamushi*), is widely distributed over an area which includes Japan, Malaya, French Indo-China, Sumatra, the Philippines, other islands of the Pacific and northern Australia. The disease will continue to be brought to the attention of physicians in the United States by returned soldiers who have residual manifestations and may again be encountered among the occupation troops in the islands of Japan.

Numerous clinical investigations have been made since the first description of tsutsugamushi by Palm in 1878. Although frequent references to neurologic and psychiatric manifestations of the disease have been made, no adequate study of the lesions of the central nervous system has been published. The present report is based on observations on a group of American soldiers and Marines during an outbreak of the disease on Goodenough Island in the D'Entrecasteaux group off the northern coast of the eastern tip of New Guinea.

### GENERAL CLINICAL OBSERVATIONS

Fifty-one patients were studied. The most common presenting complaints were severe frontal headache, malaise, anorexia, nausea and vomiting. Every one of these patients had headache. All but 5 had anorexia. Twenty-eight had nausea, and 22 had vomiting. An eschar was demonstrable in 39 patients. The course of the disease showed great variability. Bronchial symptoms with a nonproductive cough, pneumonia, faint heart sounds, evidences of mild renal involvement, enlargement and, often, tenderness of the liver and spleen, generalized

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lymphadenopathy, especially prominent in the regional nodes draining the site of the eschar, maculopapular eruption, congestion of the vessels of the conjunctiva and leukopenia were common features. Some presented tachycardia, while others showed a relatively slight elevation of pulse rate considering the degree of fever. Sustained elevations of temperature, of from 104 to 105 F, and sometimes rising to 106 or 107 F, lasted from ten to fourteen days. Two patients had a terminal rise to 108 F. Of the 39 patients whose serum gave a Weil-Felix reaction with the OXK strain of *Proteus vulgaris*, 35 had agglutinations in dilutions of 1:80 or above.

The variation in the clinical course is illustrated by case studies.

#### CASE STUDIES

CASE 1—This case is characteristic of the mild form of the disease, with rapid and complete recovery.

A man aged 35 had an onset characterized by eschar, headache, nausea and tinnitus. The course of the disease was mild. The temperature did not rise above 103 F. The Weil-Felix reaction was positive in a dilution of 1:1,280 on the fourteenth day. On getting out of bed he had considerable dizziness and weakness. His weight had fallen from 175 to 155 pounds (79.5 to 70 Kg). He steadily gained in strength and weight. Although he had no delirium and seemed fairly clear during the acute phase of his illness, he stated that for several days "things seemed hazy" and that he later did not remember what happened during this period. Two months after the onset of his illness he had no residual manifestations.

CASE 2—This case illustrates the severe headache, prostration, deafness, tinnitus and mental depression commonly encountered. Recovery was slow but complete.

A man aged 26 first became sick on Nov. 24, 1943, and his illness ran a stormy, acute course. He had an eschar on the penis, generalized lymphadenopathy, anorexia, prostration, maculopapular rash, deafness, tinnitus, bilateral bronchopneumonia and delirium. Generalized edema lasted for several days. His weight fell from 155 to 130 pounds (70 to 59 Kg). On December 2, while he was semi-delirious, his headache was very severe. Symptomatic relief was obtained by the slow withdrawal of 15 cc of cerebrospinal fluid, which was under increased pressure, contained 11 mononuclear cells per cubic millimeter and gave a 1 plus Pandy reaction. By Jan. 20, 1944 he had regained 10 pounds (4.5 Kg), slept well and had amnesia for the acute phase of his sickness. He felt depressed and was easily irritated. On May 7, after returning from a sick furlough in Australia, he felt well except for slight tremor of the hands and lack of "pep and energy." In August 1945 there was no evidence of residual symptoms.

CASE 3—Prolonged delirium was followed by persistence of difficulty in concentration and interference with original thinking eighteen months after the acute phase of the illness.

A man aged 27 was taken sick on Nov. 18, 1943. He rapidly went into a delirium, during which he talked of swimming and lying on the bottom of the ocean. At times he felt that he had died and that his wife had collected his \$10,000 insurance. Cheyne-Stokes respirations appeared, and severe, prolonged hiccups were present. By December 8 he was in an apathetic state and remarked

that he did not care whether he lived or died. During the next two months he felt weak, experienced difficulty in concentration and expressed feelings of unreality. In March 1944 he went to the mess hall and did not discover that he had left his mess gear in the ward until he returned from dinner. On contemplating what had happened, he then realized that he had had a cup of coffee instead of a complete meal. While on sick furlough, in March and April, his strength and thinking capacity improved. Feelings of unreality disappeared. When interviewed on May 7 he had the following symptoms: lack of energy and ambition, headaches and dizziness in the morning, slowness of thinking, mildly defective memory and diminished capacity to carry out original and imaginative thinking. Although he formerly had been able to write articles in Polish for a newspaper, the thoughts he put on paper were silly and disconnected. (He had spoken no English until he came to the United States, at the age of 22.) In March 1945 he felt that he had not recovered completely. He noted difficulty in concentration and in writing simple letters, was restless, lost his temper easily and felt that his powers of original thinking had deteriorated.

**CASE 4**—This case illustrates severe neurologic involvement and clouding of the sensorium. Eighteen months after the illness there were persistence of weakness in the legs and defect in grasp of complicated thought.

A man aged 38 had a severe, acute illness with a temperature of 105 F. It was characterized by intractable headache, nausea, vomiting, deafness, impaired vision, bronchopneumonia, muscular weakness, Cheyne-Stokes breathing, pains in the ocular muscles, legs and arms, diminution of sensation to touch, pain, position and vibration in the lower extremities, hyperactivity of knee and ankle jerks, hiccups, urinary incontinence, and delirium. There was a hard, smooth, hemorrhagic patch around the limbus of the left eye. The fundus of the right eye showed a small periarterial hemorrhage on the nasal side. On recovering from the acute phase of his illness, he ate well but continued to complain of pains and weakness, particularly in the legs. He spoke of the acute phase of his illness as follows: "For three weeks I had strange feelings and did not know anything. I thought I was a prisoner and tried to get away. I got out of bed several times. I had an idea my body wasn't whole and my legs were separated. I heard bells ringing." Eighteen months later he noted weakness in the legs, slowness of thinking and difficulty in grasping complicated thoughts.

**CASE 5**—This case was characterized by severe neurologic and psychiatric symptoms with recovery except for easy fatigue and memory defect.

A man aged 25 had a severe febrile stage of his illness without evidence of pulmonary or cardiac complications. It was characterized by difficulty in swallowing, in enunciation and in extending his tongue. The jacket used to shade a lamp was interpreted as a piece of fresh meat, and an attempt was made to secure it. A railroad train with hungry people, a beautiful Australian girl and cows and pigs as passengers was seen traveling under his mosquito net. At times he had muscular twitching. For three weeks evidences of neurologic involvement persisted. For several months he continued to feel weakness in his legs and to have mild feelings of unreality and difficulty in memory and concentration. Eighteen months after the acute phase of his illness he noted easy fatigue and interference with recent memory.

**CASE 6**—The case was characterized by delirium, which persisted after the febrile stage, and features of a Korsakoff syndrome, with residual thinking difficulty and feelings of unreality.

A 22 year old private in the Marine Corps had a severe febrile phase of the illness lasting two weeks, and delirium, persisting for a week after the fever had subsided. For several weeks he had pains in the legs. He was taken sick on Dec 8, 1943. Shortly after admission he began to feel that he had been moved from one ward to another. He had ideas that he had wandered from the hospital to the beach, where he fixed an airplane, flew to a recently invaded island, strafed the Japs and prepared the way for the landing of the Marines. He wrecked his plane, escaped by submarine assisted by a Chinese boy, sank much Jap shipping, lost his submarine, escaped in another boat to Goodenough Island, bought and distributed fresh foods with the help of fuzzy-wuzzies, carried out various exploits in a Marine Corps airplane, was made a major in the air corps and was so successful that he was promoted to be a three star admiral, in command of the battleship North Carolina. A prominent movie star was executive officer. The patient's temperature returned to normal on Jan 3, 1944, but evidences of disorientation, defective memory and confabulation persisted. By the end of January he had considerable insight into his mental abnormalities but had difficulty in concentration and frequently saw images of people. This he appreciated as unusual. For many years he had been interested in boats and airplanes. He realized that his ideas about flying and sailing were determined by his hobbies. He was anxious to discuss the origin of the delusions and was greatly relieved as he gained insight into them. By the middle of April he felt well physically but had some difficulty in thinking and periods when his surroundings seemed unnatural.

CASE 7—This case illustrates a severe course, with slow disappearance of neuropsychiatric symptoms and persistence of tachycardia and pain in the left upper abdominal quadrant, which may have been secondary to a splenic infarct.

A man aged 24 was taken ill on Dec 4, 1943. His illness had a severe, febrile course with delirium, tachycardia, faint heart sounds, rales at the bases of both lungs and severe pain in the left upper quadrant. Anorexia persisted for several weeks. His weight fell from 192 to 160 pounds (87 to 72.6 Kg). During his delirium he became frightened, thought that he was constantly walking with a beautiful girl and was suspicious that the personnel of his organization had turned against him. After subsidence of the delirium, he experienced violent nightmares of running away from Japs or Indians, of being chased by an old woman and of climbing an endless staircase. He had episodes of irritability, generalized trembling and excessive sweating. By the middle of February 1944 he was feeling well except for difficulty in remembering several things at one time. For example, when he had to deliver charts to two wards, it required great effort to keep in mind the numbers of these two wards. He gained in strength and alertness during a sick furlough to Australia, lasting from March 2 to April 6, 1944. There was a return of sexual desire, the loss of which had caused him considerable concern for two months. Six months after the onset of his illness he had difficulty in concentration, slowness in thinking, tachycardia and pain in the splenic region. By August 1945 he felt well physically except for persistence of the pain in the left upper quadrant. His resting pulse was 110 a minute. He had continued at duty as a guard. He felt that he was not so sharp in originating thought as he had been before his illness. "I now grope for words. At one time I was president of a debating team and had no trouble with my speech or writing. I sleep lightly now. I used to sleep very soundly. Until four months ago I had nightmares about a man sticking a knife in me and spilling out my intestines. I would get up, put on a light and look around my tent for him."



CASE 8—This case serves to illustrate a severe, fatal type of the disease complicated by meningitis. The characteristic pathologic changes of tsutsugamushi were found.

A man aged 23 had a severe reaction, which ended in death on the twelfth day after his admission. His illness began on April 3, 1944 with frontal headache and an eschar in the right suprapubic region. By April 5 he had a fever, slight chill, urinary frequency, photophobia, generalized muscular aches, pain on movement of his eyes and a slight, nonproductive cough. Physical examination on his admission, on April 6, showed congestion of the vessels of the conjunctivas, a temperature of 100.2 F and a necrotic, punched-out lesion surrounded by a red areola several millimeters in diameter. Generalized lymphadenopathy was noted. The white cell count was 4,900. A maculopapular rash developed on the chest and back. Six days after his admission respiration became labored and cyanosis appeared. Rales were found in both pulmonary fields. Hearing was impaired. Granular casts and albumin were found in the urine. On April 13 the Weil-Felix reaction was positive in a dilution of 1:40, and on April 17, in a dilution of 1:320. By April 15 he had severe hiccups, frequent extrasystoles and a pulse rate of 130 a minute. He became restless and irrational. He remarked that he seemed to "hear double" and that he could see his mother, father and fiancée. He had an overwhelming desire to escape from Goodenough Island, which he particularly disliked. He seemed frantic. A lumbar puncture was done, with withdrawal of 15 cc of fluid, under slightly increased pressure. It contained 17 mononuclear cells per cubic millimeter, and the total protein measured 29 mg per hundred cubic centimeters. The next day the patient became excited and overtalkative, his temperature rose to 105 F, his pulse and blood pressure were unobtainable, and the illness terminated fatally.

Postmortem examination<sup>1</sup> showed diffuse inflammatory changes in many organs. In the lungs there were extensive dilatation of blood vessels and invasion of the alveolar walls with lymphocytes and histiocytes. The cardiac muscle fibers appeared pale, and there was infiltration of lymphocytes and histiocytes between bundles. The pulp of the spleen was hemorrhagic, many large histiocytes were seen, and erythrophagia was demonstrable. The hepatic cells were granular, and diffusion of histiocytes, lymphocytes and occasional polymorphonuclear leukocytes was seen throughout all areas and in clumps around the portal units. In the kidneys the inflammatory reaction was minimal and limited to infiltration of rare mononuclear cells in interstitial areas. The testes showed thickening of the basement membranes of the seminiferous tubules, only immature cells in spermatogenesis, congestion of the interstitial spaces and extensive infiltration with histiocytes and lymphocytes. The lymph nodes showed congestion, indistinct markings and sinusoids containing histiocytes and lymphocytes.

#### NEUROLOGIC AND PSYCHIATRIC MANIFESTATIONS

The involvement of the central nervous system in tsutsugamushi has been described<sup>2</sup> as characterized by severe giddiness and headache and later in the disease by hyperesthesia over the body, delirium at night and deafness.

1 Lieut. Col. Vernon L. Lippard, of the Medical Corps, provided the report on the pathologic examination.

2 Strong, R. P. *Stitt's Diagnosis, Prevention and Treatment of Tropical Diseases*, ed. 6, Philadelphia, The Blakiston Company, 1942, p. 981.

Reynes and Richard,<sup>3</sup> after guinea pig inoculation, isolated the rickettsia bodies from the cerebrospinal fluid. Their patient was delirious, noisy, incontinent and hiccuping. Neurologic examination revealed tremors of the face and extremities and absence of knee and ankle jerks. Three days later hiccups disappeared, and the patient presented a syndrome of spasticity with generalized hyperreflexia. After a further brief period of delirium with erotic content he recovered except for amnesia for events which occurred during and after his illness. The cerebrospinal fluid contained 14, 30 and 137 cells per cubic millimeter on three examinations. The Weil-Felix reaction with the OXK strain of *P. vulgaris* was positive in a dilution of 1:150. Ragiot and Delbove<sup>4</sup> reported diffuse cerebral involvement, particularly in the midbrain. Poinso<sup>5</sup> found stupor and delirium and selective involvement of the gray matter of the bulb and pyramidal tracts.

In epidemic typhus, which has similar pathologic lesions, severe symptoms referable to the central nervous system have been observed. Von Stockert<sup>6</sup> reported somnolence, auditory hallucinations and catalepsy, followed by restless delirium. The patient passed into a dream state, and became convinced that he had received a high decoration from the hands of Hitler. Von Stockert also noted that months after convalescence there may be serious mental disturbances, such as changes in disposition or appearance of criminal tendencies and that mental deterioration of the type found in encephalitis may be permanent.

In the present series of patients the most frequent evidences of neurologic involvement were deafness, in 34, ringing in the ears, in 26, generalized or localized bodily pains, in 25, pain on movement of the eyes, in 18, urinary incontinence, in 17, muscular twitching, in 17, impairment of vision, in 17, hiccups, in 10, meningismus, in 5, and urinary retention, in 3. Both hypoactivity and hyperactivity of the tendon reflexes were observed. Respiration was abnormal in most cases. It was usually rapid, the rate frequently rising to 40 per minute. Nine patients, of whom 5 recovered, had Cheyne-Stokes breathing. Other symptoms which were noted in a few patients were convulsions, dysphagia, dysarthria, strabismus, inequality of the pupils, nystagmus,

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3 Reynes, V., and Richard, J. Sur un cas de typhus tropical a forme nerveuse, *Bull. Soc. path. exot.* **33** 70-73 (Feb. 14) 1940.

4 Ragiot, C., and Delbove, P. Trois cas de manifestations nerveuses au cours des fièvres typho-exanthematiques observees en Cochinchine, *Bull. Soc. path. exot.* **29** 839-844 (Oct.) 1936.

5 Poinso, R. L'encephalite boutonneuse, *Presse med.* **47** 1159-1161 (July 26) 1939.

6 von Stockert, F. G. Die psychischen Storungen bei Fleckfieber, *Deutsche med. Wchnschr.* **69** 506-508 (July 9) 1943, abstracted, *Trop. Dis. Bull.* **41** 201-202 (March) 1944.

inability to protrude the tongue, hyperesthesia, anesthesia and partial to complete loss of sense of touch, pain, position and vibration

One patient who had severe neurologic manifestations on recovering from coma had intractable pins and needles sensations in his legs. Examination showed diminished sense of touch and hypersensitivity to pinprick in his feet and slightly hyperactive tendon reflexes and loss of position and vibration senses in his lower extremities. These symptoms gradually subsided over a period of several weeks. In another patient there were transient loss of position and vibration sense, severe burning in the soles of the feet, lasting about three weeks, and feelings of numbness in the left thigh, which persisted for about five weeks. Acute parkinsonism occurred in a man who had lost much weight.

Wolf<sup>7</sup> found localized myopathy occurring in 2 patients with tsutsugamushi disease during the acute phase and persisting for many months thereafter. The muscular weakness and atrophy in both patients occurred about the shoulder girdle and exhibited the characteristics of muscular dystrophy of the Landouzy-Dejerne type.

The cerebrospinal fluid of 8 patients was examined. That of 1 patient was entirely normal. In 2 patients the only abnormality was a slight elevation of its pressure. In 1 patient (case 6) the fluid contained white blood cells and 15 red blood cells per cubic millimeter. Another (case 2) had a Pandy reaction of 1 plus and a cell count of 11 mononuclear cells per cubic millimeter. For a patient who died the results of examinations of the spinal fluid were recorded as follows: (1) mononuclear cells 3 per cubic millimeter, (2) xanthochromic fluid, a Pandy reaction of 1 plus and 35 mononuclear cells per cubic millimeter, (3) a Pandy reaction of 1 plus and 5 mononuclear cells per cubic millimeter. In the fluid of another patient (case 8) who died 17 mononuclear cells per cubic millimeter were found. For a severely ill patient who survived the following values were reported: 40 mononuclear cells per cubic millimeter, a Pandy reaction of 2 plus and a total protein content of 70 mg per hundred cubic centimeters.

Cerebral function was impaired in almost every patient. Symptoms varied from periods of apathy and restlessness to severe prolonged delirium followed by residual thinking difficulty. Thirty-one patients had poor concentration, 30, loss of memory, 29, delirium, and 17, coma. Disorientation was found in 34 patients. Twenty-four had delusions, and 17 had hallucinations. One patient had a Korsakoff psychosis. During convalescence, illusions, feelings of unreality and *déjà vu* phenomena were noted. Some were emotionally complacent throughout.

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<sup>7</sup> Wolf, S. Myopathy. Localized Muscular Weakness with Atrophy of an Unusual Type Occurring Among American Soldiers in the Southwest Pacific, to be published.

their illness Twelve showed definite fear and many others some degree of anxiety Seventeen were depressed, and 7 had marked irritability

As in other conditions with toxic or anatomic involvement of the central nervous system, the personality background and emotional reactions of the patient influenced the thought content Conflict was manifested by fears of a Japanese attack, of injury to self or comrades or of disaster at home involving financial problems, deaths or infidelity of wife or sweetheart Those who had been in combat frequently relived battle experiences Paranoid ideas of being mistreated, robbed or killed were expressed A Marine who had taken part in the difficult campaign at Guadalcanal had delusions that he was on the Russian front wondering what he was going to do next Distorted ideas often were based on the immediate situation For example, when there was profuse sweating, the patient felt that he was floating on a lake, being sprinkled with dew, swimming in the ocean or being placed in a damp hole One man who was not allowed visitors felt that all men in his organization had turned against him With some, reality problems were overcome or wishes fulfilled An Alabama farmer thought he was happily driving a team of mules A man who had been overseas for over two years felt he was visiting friends and relatives Another was having a lively time at night clubs accompanied by his fiancée, who appeared to be unusually beautiful and well dressed Some heard sweet, soothing music A patient who was especially weary of canned food, of the prohibition of liquor and of the heat of the tropics during a delirium felt that he was on a cool boat going to Australia on furlough and was surrounded by a plentiful supply of beer and delicious food

In cases of the milder form of the disease, in which there was no gross evidence of abnormality during the febrile stage of the disease, there were later periods of loss of memory, ranging from one to seven days In cases of the more severe form there was amnesia for as long as four weeks Manifestations referable to the central nervous system commonly persisted after the acute phase of the illness During the severe delirium there was less variation in symptoms between day and night than in the febrile delirium which complicates such diseases as pneumonia and typhoid In a few patients previously existing psychoneurotic tendencies, such as anxiety, depression and hypochondriasis, were accentuated In many there was a loss of sexual feeling It is likely that this was due to general debility The frequent testicular involvement, with soreness, flabbiness and pain, called the patients' attention to their genitalia and created anxiety about their sexual function

Although there were few in the series of 51 patients who showed psychoneurotic symptoms of any consequence, another group of 20

patients, who had previously been hospitalized for tsutsugamushi fever at other locations in New Guinea, later came to the Ninth General Hospital, where definite manifestations of an anxiety state, hysteria, neurasthenia or hypochondriasis were found. They knew that other soldiers, who had survived the disease, had been returned to the United States as patients. Most of them had acquired the disease months before and had been in many hospitals. In their travels from place to place they had been subjected to various philosophies in regard to the proper management of their illness, had picked up much misinformation and had had ample opportunity to misinterpret the points of view to which they had been exposed. Many of their symptoms were similar to those they had experienced during the acute and the convalescent stage of tsutsugamushi. Common complaints were easy fatigue, weakness, headaches, anxiety, palpitation, tremulousness, diffuse pains and excessive somatic preoccupation. There was usually a history of a remission followed by an exacerbation when the patient was confronted with unpleasant or dangerous army duties. Some responded well to psychiatric treatment, but others did poorly, particularly those with rigid personality patterns.

The severity and dramatic nature of the symptoms and the high mortality had a terrifying effect on the men who had been exposed to the disease but did not contract it. During the outbreak at Goodenough, three or four times the usual number of men reported on sick call. Most of them were suffering from mild anxiety and hypochondriacal reactions, which subsided as soon as the incidence of the disease decreased.

#### PATHOLOGIC CHARACTERISTICS

In 1936 Lewthwaite and Savor<sup>8</sup> noted petechial hemorrhages in the heart, lungs, alimentary tract and kidneys and small perivascular infiltrations in the pons, medulla and cerebellum. The cells surrounding the blood vessels were reported as neuroglia cells and lymphocytes, and rickettsias were thought to have been demonstrated in the cells of the walls of blood vessels. Thrombus formation was noted in some of the capillaries. Wolbach<sup>9</sup> pointed out the presence of areas of necrosis in various organs and suggested that small blood vessels of the internal organs may present lesions leading to thrombosis.

In this series, postmortem examination was made in 13 cases. In 2 cases no abnormalities of the central nervous system were noted. In 3 cases there was edema of the brain with flattening of the convolutions.

8 Lewthwaite, R., and Savor, S. R. Typhus Group of Diseases in Malaya, *Brit J Exper Path* **17** 1-34 (Feb.) 1936.

9 Wolbach, S. B., in *Virus and Rickettsial Diseases*, Harvard School of Public Health, Symposium, Cambridge, Mass., Harvard University Press, 1940.

There was moderate congestion of the cerebral vessels in 3 cases. Hemorrhages into the leptomeninges were found in 4 cases. In 1 case (8) meningitis developed. Lesions similar to those found in other organs of the body were noted in the central nervous system on microscopic examination. The blood vessels were congested. There was necrosis of the media of arterioles and a perivascular infiltration of monocytes and lymphocytes. Thromboses were in various stages of early organization. Some of the neurons showed degeneration. In several cases in which the central nervous system showed no severe involvement there was a severe complicating bronchopneumonia.

Microscopic sections from case 8 were examined by Dr. S. B. Wolbach, professor of pathology at Harvard Medical School, who gave the following opinion:

I find focal lesions in the cerebellum, cerebral cortex, pons and thalamus. They are of the same general character as those associated with typhus. In this particular case they are fewer and much less abundant in the pons than with typhus, but, as in cases of typhus, there must be a great variation in distribution. The infiltration of the meninges is of about the same degree and character as with typhus, the majority of the cells being mononuclear leukocytes or monocytes. I have compared these lesions with those in typhus, and they are so similar that I am quite certain that a fairly extensive study would be necessary to bring out any differences. Certainly, any differences in cellular composition and relation of the infiltrations to capillaries and vessels of precapillary size would be quantitative, rather than qualitative. I should conclude, therefore, that the involvement of the central nervous system bears the same relation to the signs and symptoms of tsutsugamushi fever as do the lesions of the central nervous system of Rocky Mountain spotted fever and typhus to the signs and symptoms of these diseases.

#### PROGNOSIS

The fatality rate has shown much variation in different outbreaks. Dyer<sup>10</sup> reported it as about 15 per cent for persons of all ages. The prognosis is poorer with increase in age.

Evidence of severe involvement of the central nervous system during the acute phase of the disease signified a poor prognosis. Of 17 patients who were in coma, 5 recovered. Thirteen (25 per cent) of the 51 patients died. Of the 38 survivors, follow-up data were obtained by means of interview or report by letter after six months for 25 patients and after eighteen months for 24 patients. It was possible to follow 16 men closely because they were members of this hospital detachment. Nineteen of the 24 patients had continued on duty in the Pacific area. The other 5 patients had been returned to the United States for the following reasons: length of overseas service 1, malnutrition 1, psy-

<sup>10</sup> Dyer, R. E. *The Rickettsial Diseases*, J. A. M. A. **124**: 1165 (April 22) 1944.

choneurosis, 1, and an unknown reason, 1. The 2 patients with psychoneurosis had had severe emotional difficulties of many years' duration, for which they had received treatment in Army hospitals prior to contracting tsutsugamushi fever. All 24 patients were able to carry on useful work either in the Army or in civilian life.

After six months 12 patients and after eighteen months 17, including the 2 with psychoneurosis, showed no residual manifestations. The 7 patients of the 24 (29 per cent) who continued to have symptoms complained of poor concentration, memory defect, decreased ability to grasp complicated ideas, difficulty in original and imaginative thinking, easy fatigue, deafness, tremor of the extremities, pains and weakness in the legs, tachycardia, pain in the testes and splenic region and dyspnea on exertion. One patient said, "My mind feels partly withered away." Another reported, "I feel just like a burnt-out motor." Some of these symptoms may have been psychogenic. However, for the most part they were present continuously and appeared to be secondary to severe organic involvement at the time of the acute phase of the disease. When emotionally determined symptoms were not recognized and treated, chronic psychoneurotic reactions frequently developed. If recovery was incomplete after six months, the outlook for further improvement was poor. Sexual feeling returned to normal after the debilitating phase of the illness was passed. In addition to residual manifestations referable to the central nervous system cardiovascular symptoms, such as tachycardia, precordial discomfort and dyspnea, sometimes persisted.

#### TREATMENT

Since there is no specific treatment, symptomatic and supportive care is of the greatest importance. The value of convalescent serum, which was given in several cases, was questionable. Oral administration of adequate quantities of liquids as judged by the state of hydration of the patient and the urinary output seemed best in these cases. A well balanced diet of simple foods as tolerated was important in order to maintain the nutrition and strength of the patient. Tactful spoon feeding by nurses or ward men was of great help. Morphine, scopolamine and paraldehyde were the drugs of choice in the control of restlessness and insomnia. When there was evidence of severe, intractable headache, small amounts of cerebrospinal fluid were withdrawn gradually in order to give relief. During the delirium the environment was simplified as much as possible in order to lessen the bewilderment of the patient. The number of persons caring for the patient was kept at a minimum, and visitors were restricted. Simple explanations and reassurance helped to decrease perplexity and fear. During convalescence analysis of the significance of the delusional ideas increased.

the ease and confidence of the patient. Care was taken to insure gradual increase of physical and mental activity in accordance with the patient's tolerance. It may be necessary to have the patient under medical supervision for as long as six months. Attention to the personality as a whole was of value in helping the patient to return to useful work as soon as he is capable of it. Brief analysis of personality reactions, explanation of the disease and of its symptoms, reassurance and encouragement were of benefit in many cases.

#### COMMENT

In tsutsugamushi fever one is dealing with a generalized disease which may be accompanied with mild to severe involvement of the central nervous system. Neurologic and mental examinations indicate functional and structural change in the cerebrum, the brain stem and the spinal cord. In some cases the neurologic signs point exclusively to peripheral involvement. These may be the result of nutritional deficiency and may be similar to those seen in other severe or debilitating illnesses. Inadequate caloric intake together with high fever resulted in loss of weight, sometimes as high as 60 pounds (27 Kg). The period of convalescence was frequently prolonged, and recovery was sometimes incomplete. The persistence of symptoms suggested that they were due to parenchymal destruction and secondary gliosis. Personal communication with physicians in other locations in the New Guinea area where tsutsugamushi is a common disease indicated that an unusually severe form of the disease was observed at Goodenough Island and that the manifestations of involvement of the central nervous system were more prominent than in outbreaks in other cases. The cause, symptoms and pathologic changes are similar to two diseases about which more is known, namely, Rocky Mountain spotted fever and epidemic typhus.

#### SUMMARY

Neuropsychiatric observations were made on a group of 51 patients with tsutsugamushi fever during an outbreak on Goodenough Island. Mortality was 25 per cent. All patients exhibited involvement of the central nervous system, manifestations ranging widely from transient toxic cerebral symptoms to evidence of severe, widespread inflammation, resulting in coma and death. Pathologic changes in the central nervous system were similar to those found in other organs of the body and consisted of focal lesions characterized by necrosis, thrombosis and perivascular infiltration with numerous mononuclear cells, lymphocytes and plasma cells and rare polymorphonuclear leukocytes. The rate and degree of recovery varied considerably. Twenty-nine per cent of



patients on whom follow-up data were available, eighteen months after the acute phase of the disease, showed residual manifestations, most of which appeared to be secondary to organic changes of the central nervous system. None had symptoms of sufficient severity to prevent performance of useful work. During the acute illness symptomatic treatment and good nursing care were of major importance. During convalescence graduated activity under medical supervision and prompt treatment of psychoneurotic manifestations facilitated recovery. Psychotherapy, with a brief analysis of personality reactions, explanation, reassurance and encouragement, was found to be of benefit.

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# PERMEABILITY OF BLOOD-SPINAL FLUID BARRIER IN INFANTS AND IN NORMAL AND SYPHILITIC ADULTS

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**P**OSITIVE Wassermann reactions rarely occur in the spinal fluid in the absence of syphilitic involvement of the central nervous system. "False positive" reactions of the spinal fluid have been observed<sup>1</sup> in patients with meningitis of bacterial or virus origin, especially in persons with a positive Wassermann reaction of the serum, and it has been assumed that the normal barrier between the blood and the central nervous system may be impaired by the meningeal inflammation, permitting the passage of reagin from the serum into the spinal fluid. The positive Wassermann reactions of the spinal fluid of these patients reversed after the symptoms of meningitis subsided.

Lately, we examined the spinal fluid of 16 newborn infants with syphilis. In 4 infants the results were completely normal, in 4 a positive Wassermann reaction with a high cell count, a high protein value and an abnormal colloidal gold curve were found and a diagnosis of syphilitic involvement of the central nervous system was made. In 8 infants moderately positive Wassermann reactions were found, while the cell counts, protein values and colloidal gold curves were normal, these observations are not unusual in patients with long-standing or well treated neurosyphilis and are commonly interpreted as evidence of inactivity of the infection. In the newborn, however, one cannot assume that a "burnt-out," long-standing neurosyphilis has caused reagin to remain in the spinal fluid while all other signs of an active

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From the Subdepartment of Dermatology, Department of Medicine Royal Victoria Hospital (Dr Kalz), the Children's Memorial Hospital (Dr Friedman), and the University Clinic, McGill University Faculty of Medicine (Miss Schenker and Miss Fischer)

1 Scott, V, Reynolds, F W, and Mohr, C F. Biologic False Positive Spinal Fluid Wassermann Reactions Associated with Meningitis, *Am J Syph, Gonorr & Ven Dis* 28 431 (July) 1944

inflammation have subsided. These 8 infants showed a high reagin titer in the serum, the Wassermann reactions being positive in dilutions of from 100 to 300, while the spinal fluids gave positive reactions with 1 and 0.6 cc and negative reactions with 0.4 cc. This pattern is suggestive of a passive transfer of reagin from the blood into the spinal fluid.

The 4 infants for whom a diagnosis of neurosyphilis was made were treated with sulfarsphenamine in the usual dosage and showed an unexpected quick reversal of all abnormal features of the spinal fluid. Adults with early syphilis, exhibiting a pattern of the spinal fluid abnormal in all respects, do not respond quickly to therapy and require at least a year or more for complete reversal to normal. These

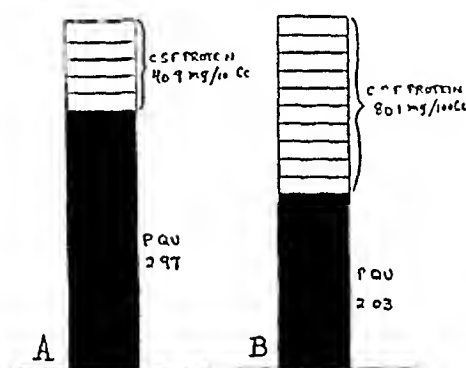


Fig 1—Graph showing the relation of the total protein content of the cerebrospinal fluid to the permeability quotient ( $P Qu$ ) of the barrier between the blood and the cerebrospinal fluid for patients with neurosyphilis ( $B$ ) and for normal (control) adults ( $A$ ). The average permeability quotient of normal patients and of patients with neurosyphilis is in inverse ratio to the amount of total protein, expressed in milligrams per hundred cubic centimeters.

4 infants, however, showed a completely normal spinal fluid within a short period. The case of 1 of these infants is reported in brief.

J. F., a French-Canadian girl, was admitted to the Children's Memorial Hospital in Montreal at the age of 2 months in a critical condition. The liver and spleen were palpable, there was severe diarrhea, and the temperature was elevated to from 101 to 103 F. A widespread, maculopapular eruption was noted, with moist papules about the anus and genitals, and brownish red, shiny infiltrations were present on the palms and soles. There were hypertrophic papules on the tongue and a purulent nasal discharge. The pupils did not react to light, the eyes did not follow moving objects, and the child appeared to be blind; ophthalmologic examination revealed prominent, edematous nerve heads. The child could not move the right arm, there was a pronounced swelling of soft tissue about the right parietal bone, and roentgenographic examination revealed destructive changes of the proximal ends of both radii, osteochondritis, zones of rarefaction, periostitis

of the long bones and a zone of rarefaction on the right parietal bone. The Wassermann reaction of the blood was positive in a dilution of 1:256. The mother was syphilitic. A diagnosis of congenital syphilis, with cutaneous, mucosal and skeletal involvement, and syphilitic neuritis of the optic nerve was made.

The general health improved quickly with transfusions, dietary adjustment and mild antisyphilitic therapy. The child was discharged after two months, completely free of symptoms and with apparently normal vision. While she was in the hospital, a total dose of 750 mg of sulfarsphenamine was given. Therapy with sulfarsphenamine and a bismuth compound was continued for one year at the treatment center of the Royal Victoria Hospital, on completion of therapy, the spinal fluid was normal in all respects, and the Wassermann reaction of the blood was negative.

The rapid improvement in the condition of the spinal fluid reflects the favorable clinical course. The laboratory data were as follows:

Date	Cells per Cu Mm	Pandy Reac- tion	Protein Content, Mg per 100 Cc	Wassermann Reaction	Colloidal Gold Curve
12/28/43	95	+	123	+ with 0.2 cc	Not determined
1/9/44	75	+	77	+ with 0.2 cc	1 1½ 2 2 2 2½ 1 0 0 0
3/8/44	2	—	27	— with 1.0 cc	Normal

The unusually quick reversal of the spinal fluid to normal in this case may be explained by assuming that the arsenical level in the spinal fluid of very young children treated with trivalent arsenicals is higher than that in adults because the barrier between the blood and the spinal fluid is undeveloped.

The relation of the spinal fluid to the blood has been treated in an exhaustive and masterly way by Katzenelbogen<sup>2</sup> in his monograph which contains a complete bibliography up to 1936. He cites the following work: Stern and Peyrat found that crystalloids pass freely from the blood into the spinal fluid in newborn animals in which the central nervous system does not reach maturity at birth, such as dogs, cats, rats, mice and rabbits, and that as the animals grow the resistance of the barrier gradually increases. The newborn guinea pig shows the same permeability of the barrier at birth as does the mature animal. Robinson found a high permeability of the barrier in newborn mice in which trypan blue was injected subcutaneously, this permeability gradually decreased as the mice grew older. Few such observations have been made on human subjects. Lenox noted increased permeability to uranium in children during the first years of life. Kriese, using Walter's bromide method, found a high perme-

<sup>2</sup> Katzenelbogen, S. *The Cerebrospinal Fluid and Its Relation to the Blood. A Physiological and Clinical Study*, Baltimore, Johns Hopkins Press, 1935.

ability in 16 of 28 children less than 3 months of age, while in older children values identical with those of adults were noted

These reports and our clinical observations previously noted, indicated that a comparison of permeability of the barrier in infants and in normal and syphilitic adults at various stages of the disease might be of interest

#### PRESENT INVESTIGATION

The bromide permeability test, devised by Walter,<sup>3</sup> was used, chiefly because it has been extensively employed in studies of patients with neurosyphilis, this test is designed to demonstrate a normal, an increased or a decreased permeability of the blood-spinal fluid barrier. Sodium bromide is given by mouth, 0.02 Gm

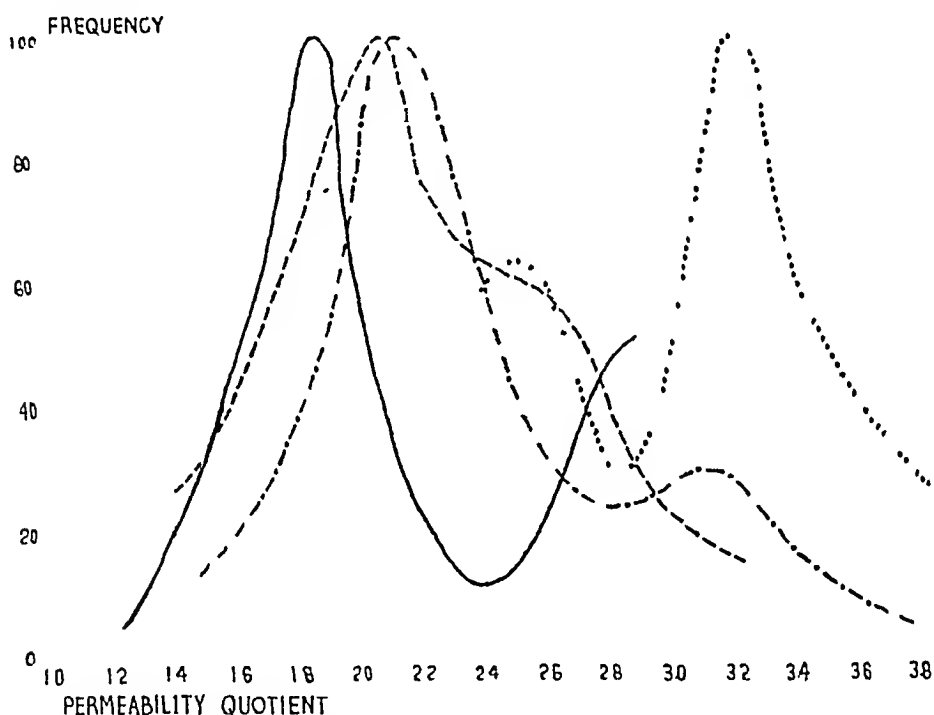


Fig 2—Frequency curves showing the probable distribution of permeability quotients for the various groups if a large number of cases were examined. The solid line indicates the curve for patients with active neurosyphilis, the broken line, the curve for normal infants, the line of dots and dashes, the curve for patients with treated neurosyphilis, and the lines of dots, the curve for normal adults. The results suggest that the differences are statistically significant. The height of the curve was chosen arbitrarily. This graph is presented through the courtesy of Dr S G Bauer, Cambridge, England, now with the Canadian National Research Council.

per kilogram of body weight, three times a day for five days. Later investigators increased the dose to 0.04 Gm per kilogram of body weight, this dose was used for the adults in our series. On the sixth day the bromide concentrations of the blood and the spinal fluid are determined. The ratio of bromide in the blood

<sup>3</sup> Walter, F K. *Die Blut-Liquorsehranke*, Leipzig, Georg Thieme, 1929

to that in the cerebrospinal fluid is called the bromide permeability quotient. Walter found that the normal range of permeability quotients was from 2.90 to 3.50. These values, with slight variation, have been corroborated by other authors. The permeability quotient for neurosyphilis was found to be significantly lower, and Katzenelbogen<sup>2</sup> presented tabulated values to this effect, in which he compared the results of various authors.

The bromide content of the blood should be higher than 30 mg per hundred cubic centimeters to insure an accurate determination, and cases in which the concentration was lower were not included in our series. To achieve this concentration in the blood in infants, we found it necessary to increase the single dose of sodium bromide to 0.2 Gm per kilogram of body weight, an amount which is five times that for adults but still well below the toxic dose.

In order to adopt the colorimetric method of Walter for the estimation of bromides to the photoelectric colorimeter, it was necessary to change the dilutions of the standards and of the blood.

*Standard Curve*—A calibration curve was made with known amounts of bromide. Thus, 143 mg of sodium bromide is dissolved in distilled water, and the solution is made up to a volume of 100 cc. Standards containing 0.5, 0.75, 1, 1.5 and 2.55 cc of the stock solution, equivalent, respectively, to 0.55, 0.83, 1.11, 1.66 and 2.77 mg of bromine, are made up to a volume of 12 cc with a 3 per cent solution of trichloroacetic acid. To each of these standards is added 2.4 cc of a 0.5 per cent solution of gold chloride (Merck's acid brown), and readings are made on the Evelyn colorimeter, using filter 520. Within this range of concentrations a rectilinear curve is obtained, and a  $K_2$  value, according to Beer's law, of  $0.1245 \pm 0.03$  is determined.

*Procedure for Blood Serum*—First, 3 cc of serum is diluted with 9 cc of distilled water. For each cubic centimeter of diluted serum 0.2 cc of a 20 per cent solution of trichloroacetic acid is added. Precipitation is allowed to take place, and the solution is filtered at the end of thirty minutes. To 6 cc of the filtrate 6 cc of a 3 per cent solution of trichloroacetic acid and 2.4 cc of a 0.5 per cent solution of gold chloride are added. The solution is then read in the photoelectric colorimeter with filter 520.

The results may be read off the calibration curve, or a  $K_2$  value based on the calibration curve may be determined for each colorimeter. If the concentration of sodium bromide in serum exceeds 125 mg per hundred cubic centimeters, the final solution should be diluted with distilled water.

It was not found necessary to allow for adsorption of bromide in the precipitated protein, as Diethelm<sup>4</sup> suggested. With the method described, the following recoveries of sodium bromide added to serum were obtained:

Serum Bromide,* Mg /100 Cc	Calculated Recovery of Bromide Mg /100 Cc	Percentage of Recovery
92.5	92.9	99.6
44.4	46.6	95.3
95.5	92.9	102.8
34.6	33.7	102.7
93.4	92.9	100.5
54.9	55.9	98.2
95.0	89.2	106.5
61.7	67.0	96.5

\* It was assumed that normal serum contained 0.4 mg of sodium bromide per hundred cubic centimeters.

*Procedure for Cerebrospinal Fluid*—To 4 cc of cerebrospinal fluid 4 cc of distilled water and 16 cc of a 20 per cent solution of trichloroacetic acid are added. The solution is allowed to stand for thirty minutes and then filtered. To 6 cc of the filtrate 6 cc of a 3 per cent solution of trichloroacetic acid is added, and the solution is read in the colorimeter as previously described. The result obtained with this dilution must be divided by 2, since the concentration of cerebrospinal fluid in the filtrate is twice that of the serum. The cerebrospinal fluid is not diluted so much as the serum, because the bromide concentration of the cerebrospinal fluid is usually much lower than that of the serum and a galvanometric reading above 80 is thus avoided.

*Clinical Material*—The following groups of patients were tested: (1) adults showing no involvement of the central nervous system, referred to as "normal adults", (2) adults with untreated neurosyphilis, referred to as patients with

TABLE 1—*Barrier Permeability in 14 Adults Without Clinical or Laboratory Evidence of Neurosyphilis*

Sex	Age	Diagnosis	Cerebro spinal fluid Protein, Mg per 100 Cc	Blood Bromide, Mg per 100 Cc	Cerebro spinal fluid Bromide, Mg per 100 Cc	Bromide Permea- bility Quotient
F	32	Syphilis, latent, late	44.6	86.2	40.6	2.12
F	24	Syphilis, latent early	58.8	80.5	36.7	2.19
F	20	Syphilis latent, late	36.1	114.7	50.0	2.29
M	30	Syphilis, latent early	50.9	68.0	26.2	2.60
F	23	Syphilis, latent, late	47.4	47.9	18.4	2.60
F	47	Syphilis, latent, late	28.4	48.2	18.4	2.62
F	31	Syphilis, secondary, treated	31.9	44.0	14.0	3.14
F	42	Syphilis, latent late	33.8	128.0	40.6	3.15
F	41	Syphilis, latent, early	26.3	83.3	26.3	3.17
M	55	Eczema	40.0	53.3	16.6	3.21
F	40	Syphilis, latent late	61.0	75.0	23.0	3.26
F	36	Syphilis, latent, late	58.4	61.0	17.0	3.39
F	33	Syphilis, congenital, inactive	36.4	36.5	9.7	3.76
F	21	Syphilis, latent, early	38.5	122.0	31.0	3.94
Average values			40.9			2.97*

\* The average permeability quotient found in this group, 2.97, is well within the limits of values described as normal.

"active neurosyphilis", (3) adults with neurosyphilis who have received at least one year of treatment, fever therapy and/or treatment with pentavalent arsenicals, referred to as persons with "inactive neurosyphilis," and (4) infants less than 18 months of age who were nonsyphilitic, referred to as "normal infants."

#### COMMENT

Our observations on increased permeability of the barrier between the blood and the spinal fluid in infants may explain the positive Wassermann reaction of the spinal fluid of infants with congenital syphilis who otherwise show no signs of neurosyphilis, this increased

TABLE 2—*Barrier Permeability in 9 Adults with Active Neurosyphilis*

Sex	Age	Type of Neurosyphilis	Cerebrospinal Fluid Wassermann Reaction					Colloidal Gold Curve	Cell Count	Pandy Reaction	Cerebrospinal Fluid Protein, Mg per 100 Cc	Blood Bromide, Mg per 100 Cc	Cerebrospinal Fluid Bromide, Mg per 100 Cc	Bromide Permeability Quotient	
			1 Cc	0.6 Cc	0.4 Cc	0.2 Cc	0.1 Cc								
M	62	Asymptomatic, group 3	+	+	+	+	±	5 5 5 5 3 2 1 0 0	200	+	109.2	97.2	89.0	1.09	
M	59	Tabes dorsalis	+	+	+	+	+	5 5 5 5 3 2 1 0 0	8	0	69.2	65.5	36.7	1.78	
M	51	Asymptomatic, group 3	+	+	+	+	+	5 5 5 5 5 2 1 0 0			97.2	62.8	34.6	1.82	
M	58	Asymptomatic, group 3	+	+	+	+	0	1½ 1½ 2 3½ 3 2 ½ 0 0 0	2	0	72.1	101.0	55.2	1.83	
F	32	Dementia paralytica	+	+	+	+	+	4½ 5 4 3 3 1½ 0 0 0 0	5	0	39.2	58.6	31.2	1.88	
M	41	Asymptomatic, group 2	+		±	0	0	½ 1½ 1½ 2 2½ 1½ ½ 0 0 0	2	0	83.1	101.0	47.8	2.11	
F	53	Asymptomatic, group 3	+	+	+	+	+	5 5 5 4½ 3 2 1 ½ 0 0	2	+	86.8	42.9	20.3	2.11	
F	39	Asymptomatic, group 1	±	0	0	0	0	Normal	4	0	83.4	60.8	22.3	2.73	
M	29	Asymptomatic, group 2	+	+	±	0	0	1½ 4 3 3 1 0 0 0 0	0	0		52.0	18.0	2.89	
Average values												80.1			2.03*

\* The average permeability quotient found in this group is in agreement with the values of various authors for patients with untreated neurosyphilis



permeability of the barrier may permit the passage of reagin from blood into the spinal fluid

Increased penetration of arsenicals into the spinal fluid may explain the unusually quick serologic reversal and the clinical cure of the active neurosyphilis in infants under routine therapy

Increased permeability of the barrier in infants may be a phenomenon meriting further studies, especially with regard to therapy with penicillin

TABLE 3—*Barrier Permeability in 22 Nonsyphilitic Infants*

Sex	Age	Diagnosis	Blood Bromide, Mg per 100 Cc	Cerebro spinal fluid Bromide, Mg per 100 Cc	Bromide Permea- bility Quotient
M	17 mo	Pneumonia anemia	14.4	36.7	1.21
F	18 mo	Pneumonia, anemia	150.0	113.0	1.33
M	3 wk	Intoxication	97.4	66.0	1.48
M	3 mo	Pneumonia, convalescent	165.0	88.9	1.74
F	5 wk	Infection of upper respiratory tract	196.0	110.5	1.77
M	4 mo	Rickets congenital heart disease, otitis media	125.0	69.8	1.79
M	4 mo	Infection of upper respiratory tract	84.0	42.9	1.96
M	12 mo	Lobar pneumonia	151.5	78.2	1.98
F	13 mo	Infection of upper respiratory tract	100.2	50.4	1.99
F	13 mo	Pneumonia convalescent	72.3	36.1	2.00
M	3 mo	Pneumonia, convalescent	83.6	41.5	2.01
M	3½ mo	Pneumonia otitis media	120.0	55.6	2.16
F	2 mo	No disease	97.1	44.6	2.18
F	23 mo	Pneumonia convalescent	85.2	36.4	2.34
F	4 mo	Otitis media	50.5	20.7	2.44
M	14 mo	Nutritional anemia	75.1	30.4	2.47
M	5½ mo	Eczema	86.2	32.4	2.66
F	4 mo	Otitis media	66.0	24.4	2.70
M	15 mo	Nutritional anemia, infection of upper respiratory tract	87.0	30.4	2.86
F	5 mo	Otitis media	31.9	11.1	2.87
M	3 mo	Tracheobronchitis, convalescent	49.4	15.2	3.25
M	5 wk	Infection of upper respiratory tract	36.6	10.8	3.39
Average value					2.21*

\* The average permeability quotient for this group of normal infants is significantly lower than the values listed for adults and closely approaches the figures found for adults with neurosyphilis

# SUMMARY

The permeability of the blood-spinal fluid barrier was determined for nonsyphilitic infants and was compared with that for normal adults and for adults with neurosyphilis. The values for infants were significantly lower than those for adults and were comparable to the values for adults with neurosyphilis.

Walter's bromide method was used for this investigation, and adaptation of this method to photoelectric readings is described.

TABLE 4—Barrier Permeability in 31 Adults with Well Treated and Inactive Neurosyphilis

Sex	Age	Type of Neurosyphilis	Cerebrospinal Fluid Wassermann Reaction						Colloidal Gold Curve	Cell Count	Pandy Reaction	Cerebrospinal Fluid Protein, Mg per 100 Cc	Blood Bro- mide, Mg per 100 Cc	Cerebro- spinal Fluid Bromide, mg per 100 Cc	Bromide, Permea- bility Quo- tient
			1 Cc	0.6 Cc	0.4 Cc	0.2 Cc	0.1 Cc	Cc							
M	52	Diffuse vascular with epilepsy	+	+	±	±	0	0 ½ 1 2 2 1 ½ 0 0 0	2	0	80.4	47.6	33.5	1.42	
M	53	Meningovascular	+	+	+	+	+	1 1 ½ 1 ½ 2 1 ½ ½ 0 0 0	2	0	107.6	114.7	71.1	1.61	
M	46	Asymptomatic, group 1	0	0	0	0	0	Normal	0	0	42.0	46.0	26.5	1.73	
F	52	Meningovascular	+	+	±	0	0	Normal	0	0	80.2	90.7	47.8	1.90	
M	59	Meningovascular	+	±	±	±	0	0 ½ 2 1 0 0 0 0 0	—	—	100.6	30.0	15.5	1.94	
F	48	Meningovascular	+	±	0	0	0	Normal	0	0	36.4	56.2	28.9	1.94	
M	46	Meningovascular	+	+	+	+	±	½ 1 ½ 2 1 0 0 0 0 0	3	0	74.0	59.6	30.5	1.95	
M	48	Meningovascular	+	+	±	0	0	Normal	1	0	56.4	60.0	30.0	2.00	
F	42	Dementia paralytica	+	+	±	±	0	1 ½ 1 ½ 2 2 1 0 0 0 0	2	0	75.6	123.0	59.8	2.06	
M	53	Tabs dorsalis	0	0	0	0	0	Normal	0	0	78.8	125.5	59.6	2.11	
M	49	Dementia paralytica	+	+	+	+	±	Normal	2	0	38.6	53.5	25.2	2.12	
F	59	Tabetic dementia paralytica	+	+	+	+	+	2 ½ 4 4 4 ½ 3 1 ½ ½ 0 0 0	5	0	38.7	37.5	31.2	2.13	
M	48	Meningovascular	+	+	+	+	+	1 ½ 2 2 1 ½ ½ 0 0 0 0	2	0	40.0	62.5	27.7	2.14	
F	37	Asymptomatic, group 2	+	+	+	+	0	Normal	0	0	38.7	37.5	17.5	2.26	
M	44	Meningovascular	+	+	±	±	0	Normal	1	0	64.6	68.4	30.3	2.26	
M	58	Asymptomatic, group 1	±	0	0	0	0	Normal	0	0	67.6	80.5	35.6	2.26	
M	41	Meningovascular	+	+	+	+	+	5 5 4 ½ 3 2 1 0 0 0 0	0	0	21.6	62.5	27.7	2.26	
M	67	Tabs dorsalis	+	±	±	0	0	Normal	0	0	63.2	84.9	36.7	2.31	
F	35	Meningovascular with epilepsy	+	+	+	+	+	½ 2 3 2 1 ½ 0 0 0 0	0	0	48.0	48.0	20.1	2.35	
M	38	Dementia paralytica	+	+	+	+	+	5 5 5 5 5 4 1 ½ 1 0	6	0	83.4	65.2	22.3	2.43	
M	44	Tabs dorsalis	+	+	±	0	0	1 ½ 1 ½ 1 ½ 3 ½ 3 2 1 ½ 0 0 0	2	0	61.8	91.0	36.1	2.52	
M	49	Asymptomatic, group 2	±	0	0	0	0	Normal	2	0	74.0	100.0	38.9	2.57	
F	27	Asymptomatic, group 3	+	+	+	+	±	1 ½ 2 ½ ½ 0 0 0 0 0	2	0	70.8	52.6	18.1	2.86	
M	49	Meningovascular	+	+	+	+	+	1 ½ 1 ½ 2 3 2 ½ 1 0 0 0 0	2	0	47.4	53.6	18.0	2.94	
F	22	Asymptomatic, group 1, early	0	0	0	0	0	Normal	2	0	31.5	112.0	38.0	2.95	
M	41	Meningovascular	+	+	±	±	0	2 ½ 2 ½ 3 2 1 ½ 1 0 0 0 0	2	0	71.2	73.8	21.6	3.00	
M	41	Meningovascular	+	+	±	±	0	1 ½ 2 1 ½ 1 ½ 0 0 0 0	0	0	51.1	54.0	17.0	3.18	
F	42	Asymptomatic, group 3	+	+	+	+	+	0 ½ 1 1 ½ 2 1 ½ 0 0 0 0	0	0	53.0	60.6	18.1	3.29	
F	27	Asymptomatic, group 1	0	0	0	0	0	Normal	2	0	58.4	165.0	50.0	3.30	
M	43	Dementia paralytica and optic nerve atrophy	+	+	+	+	+	1 ½ 1 ½ 4 ½ 4 2 ½ 1 ½ ½ 0 0 0	2	+	49.5	50.0	12.0	4.17	
F	40	Asymptomatic, group 3	+	+	+	+	+	1 1 ½ 3 2 ½ 2 0 0 0 0 0	0	0	51.9	125.0	30.0	4.17	
		Average values							60.7*						2.46*

\* The average permeability quotient and the total protein values for this group lie between the figures listed for adults and active neurosyphilis and for normal adults

These observations explain positive Wassermann reactions of the spinal fluid of syphilitic infants who otherwise show no evidence of neurosyphilis, clinically or with laboratory tests

It is suggested that positive Wassermann reactions of the cerebrospinal fluid of syphilitic infants should not be considered proof of neurosyphilis in the absence of other evidence

Miss Barbara Dean, Department of Dermatology, Royal Victoria Hospital, prepared the tables

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# USE OF QUANTITATIVE PARASITE INOCULATION DOSES IN PLASMODIUM VIVAX MALARIA THERAPY

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CUMULATIVE experience with therapeutic malaria in the management of neurosyphilis during the past twenty-five years has resulted in refinement of technics and in a clearer understanding of the characteristics of induced malarial infection. The febrile course of *Plasmodium vivax* malaria, following either natural or artificial inoculation, in most instances does not display the regular tertian paroxysms commonly described in textbooks. The majority of infections exhibit quotidian cycles with varying degrees of irregularity. At the onset of clinical activity, following mosquito inoculation or the usual administration of a 5 to 10 cc inoculum of blood at institutions utilizing therapeutic malaria, a period of several days of remittent fever, characterized by continuous low grade elevations of temperature, to 101 or 103 F, is experienced. This period of remittent fever is commonly accompanied with severe malaise and exhaustion, often debilitating the patient prior to the establishment of true malarial paroxysms. Since the accepted criterion for determining the therapeutically effective amount and duration of fever therapy of neurosyphilis consists either in the number of paroxysms reaching 104 F or more or in the number of hours of fever experienced at a temperature above 103.6 F, the period of remittent fever, exhausting the patient before clinical activity is regulated, contributes little to the therapeutic course.

Investigators in malaria research consider this initial period of remittent fever the result of asynchronization of different broods of malaria parasites. This asynchronization of parasites following intravenous inoculation is apparently produced by the injection of a large number of organisms in different stages of schizogony, resulting in remittent fever when clinical levels of parasitemia are reached. Synchronization of these broods occurs only after several days of clinical activity has permitted domination by a single brood and cycle.

It was the purpose of the investigation here reported to control the technics of inoculation in order to eliminate the disturbing period of remittent fever and to have as many patients as possible experience paroxysms of therapeutic benefit at the onset of clinical activity. It seemed logical that if a single parasite were injected into a recipient's blood stream, only one brood of parasites would mature and only one cycle of paroxysms, typically tertian, would eventuate. The inoculation of single trophozoites is now being accomplished with some degree of success at the Station for Malaria Research (Rockefeller Foundation), Tallahassee, Fla., with use of the micropipet. Such a technic requires the utmost skill, is time consuming and must be confined to research laboratories.

The quantitative parasite count, performed by a relatively simple method, has initiated a technic of inoculation based on predetermined parasite doses low enough to eliminate or suppress the period of remittent fever. Total doses of less than 500,000 parasites often require laborious dilution methods, which appreciably diminish the clinical applicability of the technic. For that reason, doses ranging from 1,000,000 to 150,000,000 parasites were used in this study. In many instances intradermal inoculation was attempted with the thought that few parasites would reach the blood stream, resulting in less asynchronization and greater regularity of the febrile response. The results of a comparative study of the duration of the period of remittent fever and the type of febrile cycle produced by the inoculation of *P. vivax* parasites intradermally, intravenously, in varying parasite doses, and by mosquito application are reported in this communication.

#### MATERIAL AND METHOD

From June 25, 1944 to Aug. 31, 1945, a total of 265 patients with neurosyphilis were inoculated with *P. vivax*. Thirty-six patients experiencing spontaneous remissions prior to the completion of a therapeutic course and requiring a course of quartan malaria therapy, or inoculation with *Plasmodium falciparum*, were excluded from this study because of their immune responses. Of the remaining 229 white patients, the results for a series of 205 were actually analyzed. The 24 patients for whom results were omitted from the analysis were those who had a definite history of previous attacks of natural malaria. This omission was justified by the observation that the period of remittent fever and the type of the paroxysmal cycle were dependent not only on the technic of inoculation but on the degree of immunity to malaria of the individual patient. A previous study of homologous and heterologous immunity to *P. vivax* malaria with the cross inoculation method<sup>1</sup> clearly indicated that the ability of a partially immunized patient to deal with injected parasites is quite different from that of a susceptible patient.

1 Kaplan, L. I., Read, H. S., and Becker, F. T. Homologous and Heterologous Strains of *Plasmodium Vivax*. A Cross-Inoculation Study of Malaria Strain Immunity, *J. Lab. & Clin. Med.* 31: 400, 1946.

*Technics of Inoculation*—1 Mosquito Inoculation Three to 6 mosquitoes from lots<sup>2</sup> of known infectivity were applied (in individual cages) to the upper extremity and axilla of 58 patients After application, each mosquito was dissected in order to determine the approximate degree of infectivity from the density of sporozoites extruded from the salivary glands In all instances a minimum of 2 infected mosquitoes per patient was considered necessary for a successful clinical "take"

2 Intradermal Inoculation Ordinary tuberculin syringes were used to inject whole blood directly from a donor into 4 wheals on the recipient's forearms (0.05 cc of blood in each wheal) Donors with parasite counts of approximately 5,000 per cubic millimeter were employed in most instances in order to give a total dose of approximately 1,000,000 to 2,000,000 parasites in the 0.2 cc of intracutaneously injected blood Twenty-six of 34 patients inoculated with this technic completed therapeutic courses, and their data were included in the analysis

3 Intravenous Inoculation The single syringe technic, with which whole blood is directly transferred from donor to recipient without the use of anti-coagulants, was employed Inoculums varied from 0.05 to 10 cc, depending on the quantitative parasite count of the donor Total doses injected with this method ranged from 1,000,000 to 150,000,000 parasites Fifty-six patients received doses of 1,000,000 to 5,000,000 parasites, 29 received 6,000,000 to 25,000,000 parasites, and 36 received 26,000,000 to 150,000,000 parasites An illustration is given

Quantitative parasite count of donor, 5,000 per cubic millimeter

Inoculum of 1 cc, 5,000,000 parasites

Inoculum of 0.2 cc, 1,000,000 parasites

Inoculum of 10 cc, 50,000,000 parasites

*The Quantitative Parasite Count*—The technic of the quantitative parasite count, Boyd's modification of that described by Earle and Perez,<sup>3</sup> may be described as follows

#### 1 Materials Required

- (a) Capillary pipets graduated to deliver 5 cu mm of blood
- (b) Glass slides on which are ruled or etched rectangles measuring 3 by 15 mm
- (c) Microscope, the ocular of which contains a Howard disk micrometer The surface of the micrometer is ruled with one large square, divided into 16 minor squares and so calibrated that with a predetermined tube length the area on a slide covered by the large square on the micrometer is known

(d) Diluted Giemsa stain

#### 2 Method

(a) Exactly 5 cu mm of blood is discharged onto the ruled rectangle of the slide, care being taken to avoid bubbles With a needle point the blood is carefully spread out to the edges and into the corners of the ruled area The film is allowed to stand in a horizontal position until dry Since 5 cu mm of blood is spread out over 45 sq mm, there will be spread over each square millimeter of the rectangle 0.11, or  $\frac{1}{9}$ , cu mm of blood

(b) The smear is stained with Giemsa's stain, as is any other thick smear, and washed, drained and dried

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2 Supplied by Dr Boyd

3 Earle, W C, and Perez, M Enumeration of Parasites in the Blood of Malarial Patients, J Lab & Clin Med 17 1124, 1932

(c) Assuming that the micrometer disk has been calibrated so that the large square covers an area of 0.01 sq mm on the slide, it will be necessary to count the parasites on the stained smear in 100 consecutive and discrete fields to estimate the parasites in the blood spread over 1 sq mm. The fields should be selected as the smear is traversed on different parallel lines. The total of the parasites counted in 100 fields will, when multiplied by 9, give the number per cubic millimeter (fig 1)

*Tabulation of Data*—This investigation was concerned chiefly with the influence of methods of inoculation on the duration and severity of the period of remittent fever at the onset of clinical malaria. Continuous days of remittent fever were

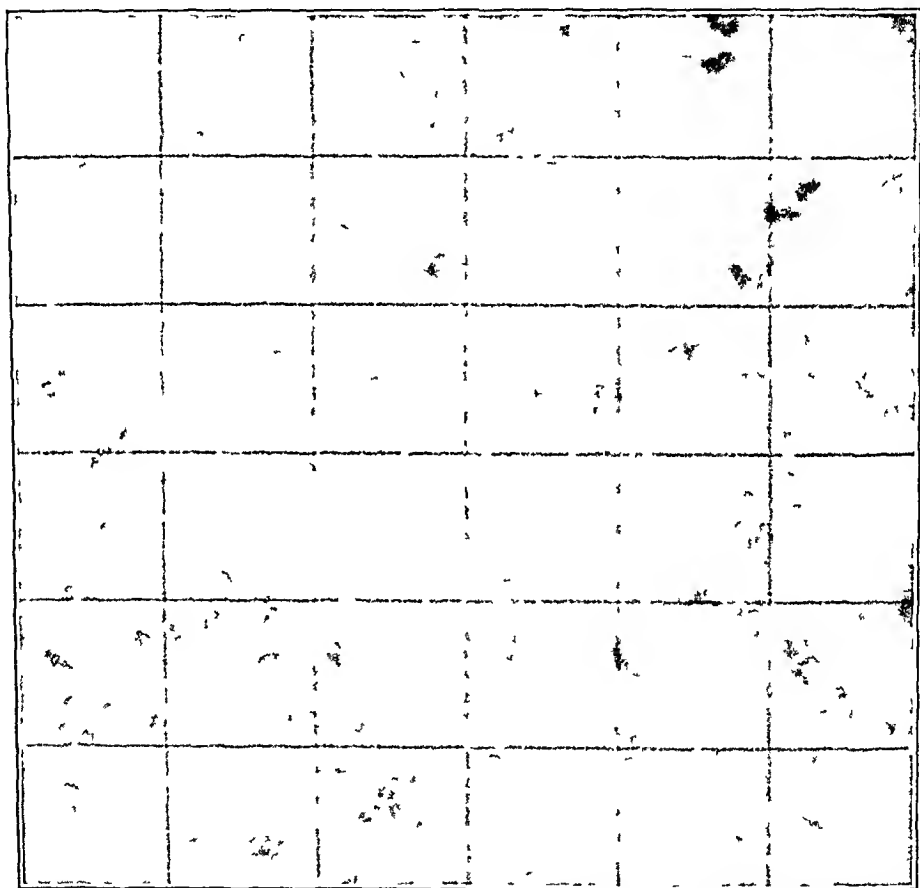


Fig 1—Microscopic field (95 magnification objective), showing parasites in a thick smear seen through the Howard disk

calculated from the time of the initial elevation of temperature above 100 F to the first normal temperature record prior to the onset of effective paroxysms. During this period no decrease in temperature below 100 F occurred. The first twenty-four hours of the period of remittent fever was excluded from the calculation in order to make it possible to tabulate no days of remittent fever for those patients initiating activity with an immediate paroxysmal cycle. Examples of febrile courses with different periods of remittent fever are illustrated in figure 2

Though variation in the technic of the inoculation did not have as significant an effect on the subsequent cycle of paroxysms as it did on the period of remittent

fever, the percentage of patients in each inoculation group exhibiting tertian paroxysms was, nevertheless, recorded. The known influence of the donor's cycle (quotidian or tertian) in predetermining the subsequent cycle in the recipient was in large part canceled by an approximately equal distribution of donors' cycles (24 to 26 per cent tertian) in each group.

Because of the regularity with which the prepatent and incubation periods are related to the parasite dose, varying inversely with the total dose administered intravenously, in such a series of susceptible patients, the duration of these periods was not recorded in this study.

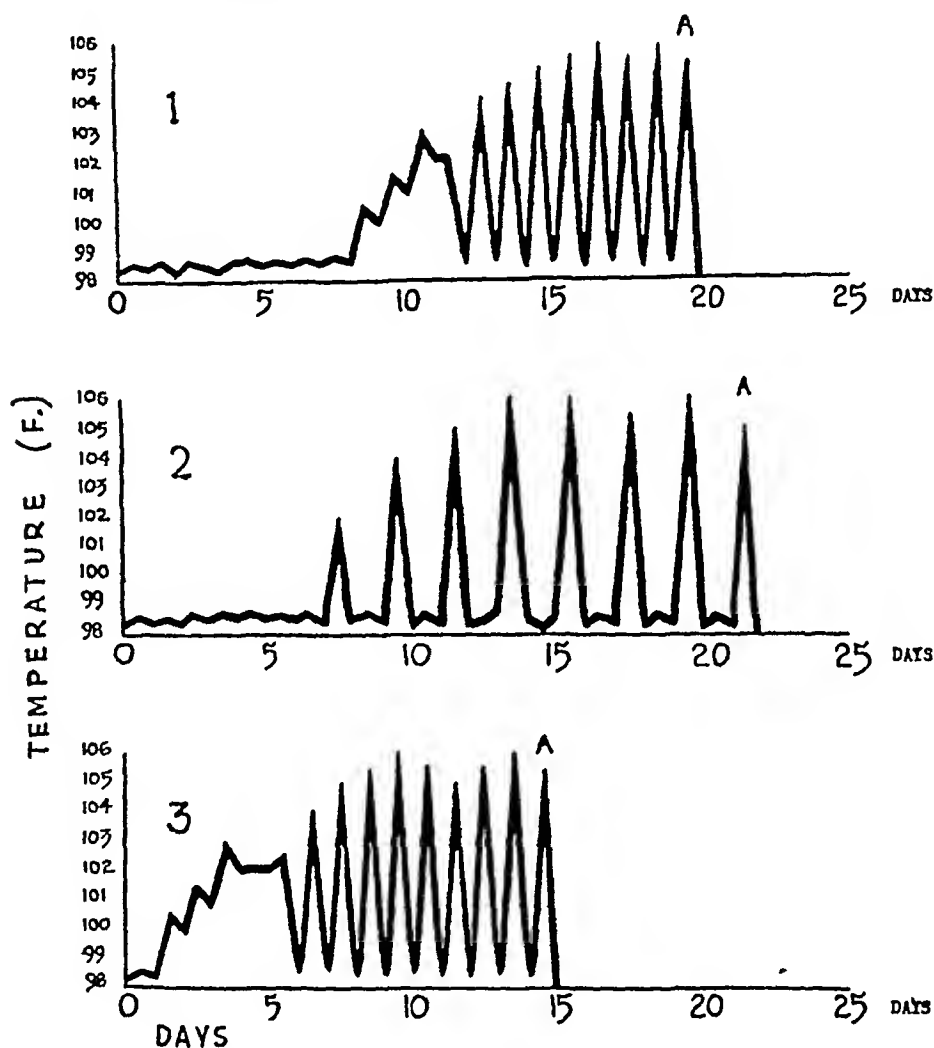


Fig 2—Febrile courses with various periods of remittent fever. Each temperature graph starts with the day of inoculation. A, at the end of each course, signifies the institution of quinine therapy. 1 shows the febrile course following mosquito inoculation (three days of remittent fever), 2, the course following intradermal inoculation (no days of remittent fever), and 3, the course following intravenous inoculation with 100,000,000 parasites (five days of remittent fever).

#### RESULTS

The data summarized in the table indicate the number of patients inoculated with each technic, the type of subsequent febrile cycles and the percentage of patients, by groups, experiencing periods of remittent



fever lasting no, one, two, three, four or five days. Figures 3 and 4 show the distribution curves for these figures. Intradermal inoculation eliminated the period of remittent fever in 42.3 per cent of the patients and resulted in periods of remittent fever lasting two days or less in 78.9 per cent. This result, as compared with the results of mosquito inoculation (8.6 per cent of patients with a period of no days of remittent fever and 37.9 per cent with two days or less of remittent fever) and

### Summary of Data

Method of Inoculation *	No. of Patients Inoculated	Percent age with Tertian Cycles	Distribution of Patients (%) by Period (Days) of Remittent Fever					
			0	1	2	3	4	5
Intradermal	26	57.8	42.3	23.1	11.5	19.3	0.0	3.8
Mosquito	38	22.4	8.6	17.2	12.1	22.8	15.6	13.8
Intravenous (1.5 M)	36	37.5	23.2	17.8	17.8	17.8	16.2	7.2
Intravenous (6-25 M)	29	31.0	13.8	10.3	11.0	24.1	13.8	7.0
Intravenous (26-150 M)	36	25.0	11.1	11.1	22.2	13.9	19.5	22.2
Intravenous (1 M)	28	42.9	35.7	17.9	11.3	11.3	14.3	3.5
Intravenous (2.5 M)	28	32.1	10.7	17.9	21.4	21.4	17.9	10.7

\* M stands for millions, e. g., 1,000,000 5,000,000

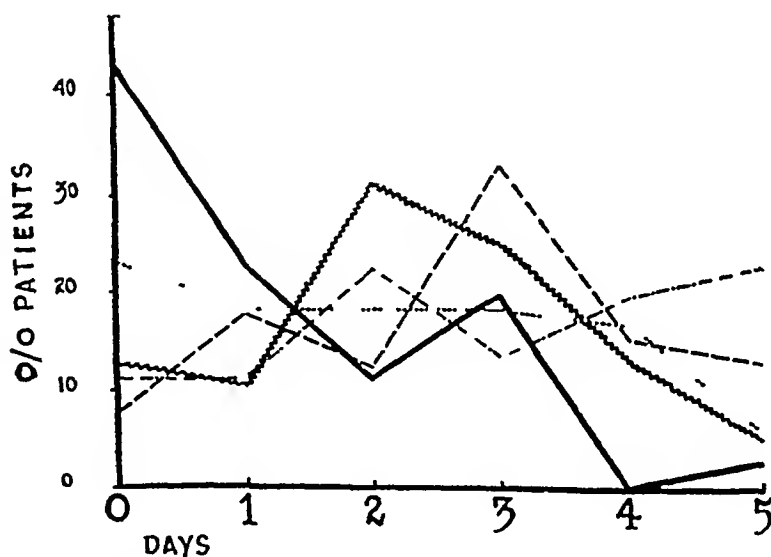


Fig. 3—Distribution curves for the duration of remittent fever with each method of inoculation. The best results are indicated by the highest percentage of patients experiencing no, one or two days of remittent fever.

In this figure, the solid line represents intradermal inoculation, the line of dashes, mosquito inoculation, the line of dots, intravenous inoculation with 1,000,000 to 5,000,000 parasites, the wavy line, intravenous inoculation with 6,000,000 to 25,000,000 parasites, and the line of dots and dashes, intravenous inoculation with 26,000,000 to 150,000,000 parasites.

with those of intravenous inoculation of 26,000,000 to 150,000,000 parasites (11.1 per cent of patients with no days of remittent fever and 44.4 per cent with remittent fever lasting two days or less), demon-

strates that the severity of the initial clinical activity in *P. vivax* malaria is significantly diminished by the employment of intradermal inoculation. However, of 34 patients originally inoculated with this method, 6 failed to exhibit clinical activity, although they demonstrated clinical responses characteristic of susceptible patients on subsequent intravenous reinoculation with the same strain of *P. vivax*. This indicated a serious technical failure, resulting probably from the unpredictable destruction of parasites before they reached the circulation. Therefore, although intradermal inoculation most satisfactorily diminishes the period of remittent fever, it cannot be recommended as a routine procedure because of the high incidence (18.8 per cent) of unsuccessful "takes" in susceptible patients. For this reason, closer attention was directed to the intravenous method of inoculation with total doses of less than 5,000,000 parasites.

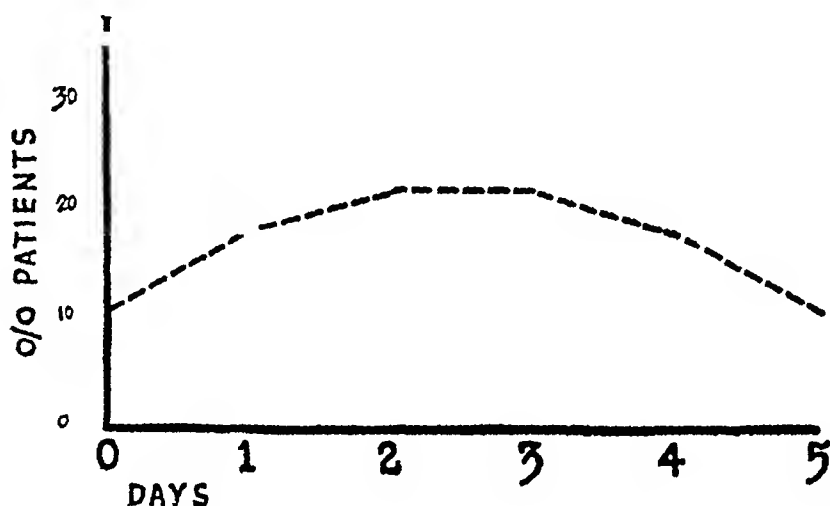


Fig 4—Distribution curves for the duration of remittent fever with intravenous inoculation of low parasite doses. The continuous line, closely simulating the curve for intradermal inoculation (fig 3), represents the results with the recommended dose of 1,000,000 parasites.

In this figure, the solid line represents intravenous inoculation with 1,000,000 parasites, and the broken line, intravenous inoculation with 2,000,000 to 5,000,000 parasites.

Mosquito inoculation, resulting in remittent fever lasting three days or longer in a high percentage of cases (62.1 per cent), has other disadvantages which limit its usefulness to hospitals and laboratories especially equipped for such procedure. The necessity for maintenance of an insectary and of technicians trained in mosquito dissection and application prohibits the adoption of this technic in many institutions intimately concerned with the treatment of neurosyphilis. The increased incidence of malaria relapses following the mosquito-induced disease as compared with the incidence following other methods of inoculation detracts further from its practicability.

Intravenous inoculations with comparatively small parasite doses (1,000,000 to 5,000,000) were followed by periods of remittent fever more severe than the periods of fever after intradermal inoculation and less severe than those following mosquito application and intravenous inoculation with heavy parasite doses (26,000,000 to 150,000,000). The period of remittent fever was absent in 23.2 per cent and lasted two days or less in 58.8 per cent of patients in this group. However, a further breakdown of this inoculation series into a group receiving inoculums of 1,000,000 parasites and another receiving 2,000,000 to 5,000,000 parasites elucidates the effect produced by progressive decrease in the parasite dose. The patients inoculated intravenously with 1,000,000 parasites exhibited a distribution curve most closely resembling the curve for intradermal inoculation, with 35.7 per cent having absence of remittent fever and 67.9 per cent experiencing two days or less (fig. 4). These observations lead one to suspect that further decrease in the intravenous parasite dose, e. g., to 100,000 parasites or less, would shorten or eliminate the period of remittent fever in a still greater percentage of patients. However, the difficulties encountered in injecting doses of less than 1,000,000 parasites intravenously, such as dilution methods, and the greater risk of technical failure seem to justify the adoption of intravenous administration of the 1,000,000 parasite dose as the most practicable method of shortening the initial, exhausting period of remittent fever of induced malaria.

Although experience with therapeutic malaria has demonstrated that the recipient's febrile cycle depends to some extent on the donor's previous cycle, an interesting result of varying the technic of inoculation was observed in this study. Tertian cycles were exhibited by 24 to 26 per cent of donors in each blood inoculation group. In spite of this relatively equal cycle distribution among donors, tertian paroxysms were experienced in the largest number of patients (57.8 per cent) in the intradermal inoculation group and in the smallest number of patients (25 per cent) in the intravenously inoculated group (26,000,000 to 150,000,000 parasites). The percentage of patients with tertian cycles following intravenous inoculation varied inversely with the parasite dose, with 42 per cent occurring in the group receiving the 1,000,000 parasite dose, 32.1 per cent in the group receiving the 2,000,000 to 5,000,000 parasite dose, 31 per cent in the group receiving the 6,000,000 to 25,000,000 parasite dose and 25 per cent in the group receiving the 26,000,000 to 150,000,000 parasite dose. These data suggest that the better tolerated tertian cycle, like the shortened period of remittent fever, is more frequently associated with intradermal inoculation and with the intravenous inoculation of 1,000,000 parasites than with the other inoculation technics.

## SUMMARY AND CONCLUSIONS

Elimination of the ordinarily long period of remittent fever initiating the clinical course of therapeutic malaria prevents the early exhaustion of patients. An elaborated investigation of the relationship of technics of inoculation to this period of remittent fever has resulted in observations of clinical value.

Intradermal inoculation was followed by the shortest and least severe period of remittent fever, with 76.9 per cent of patients experiencing fever for two days or less and 42.3 per cent not at all. However, the occurrence of 18.8 per cent of unsuccessful "takes" as a result of technical difficulties makes the routine use of this method unjustified.

Intravenous inoculations with doses ranging from 1,000,000 to 150,000,000 parasites revealed in susceptible persons that the higher the parasite dose the longer was the period of remittent fever in the greater percentage of patients. The lower the parasite dose the shorter and less severe was the remittent fever, resembling the results following intradermal inoculation.

The intravenous inoculation of 1,000,000 *P. vivax* parasites, determined by correlating the amount of inoculum with the quantitative parasite count of the donor, is recommended as a standard procedure in the therapy of neurosyphilis when one is dealing with susceptible white patients. This technic eliminated the period of remittent fever in 35.7 per cent of patients and shortened it to two days or less in 67.9 per cent of patients in this study. Similarly, if the paroxysmal cycle of the donor is disregarded, the greatest percentage of tertian cycles after intravenous inoculation will follow the employment of this parasite dose.

Mrs. Winifred Eickstaedt, Sgt. Ivan G. Strickler and Cpl. Richard P. Roy gave secretarial, laboratory and statistical aid in the preparation of this paper.

## RESISTANCE TO INSULIN IN MENTALLY DISTURBED SOLDIERS

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WORCESTER, MASS

PREVIOUS investigators<sup>1</sup> have noted abnormalities in the carbohydrate metabolism of psychotic persons. Their studies have concentrated chiefly on the response of the blood sugar to ingested dextrose, and have revealed that there exists a reduction in the dextrose tolerance, with resulting diabetic-like levels of blood sugar. To determine whether this abnormal trend is due to a dysfunction of the insulinogenic mechanisms, Freeman<sup>1a</sup> and Braceland<sup>1c</sup> investigated the insulin tolerance of schizophrenic subjects and found that such patients show a less pronounced fall in blood sugar after the administration of insulin than do normal subjects.

In order to determine whether resistance to insulin is a characteristic feature of the schizophrenic psychosis alone, I made a study of this function in other mental disorders.

### METHOD AND MATERIAL

The subjects included 93 soldiers discharged from the Army for psychiatric disorders. The average age of the patients lay between 20 and 25. Their nutrition was on the whole good, the average nutritional index being 98 per cent of the ideal (according to standards of the Metropolitan Insurance Company). Few were grossly overweight or underweight. The average stay in the Army before psychiatric symptoms appeared was six months. Each patient had been confined in a mental disease hospital in the military service for an average of two months before the present study. These patients showed many varieties of psychiatric symptoms, although in general the clinical status showed less clearly defined and more transitory types of disturbance than are ordinarily found in the civilian population.

The technic of the test was simple. After a postabsorptive period of at least fourteen hours, a control sample of blood was taken, and insulin was then administered intravenously in a dose of 0.1 unit per kilogram of body weight. Subsequent samples of blood were taken at regular thirty minute intervals, with the patient lying quietly in bed.

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From the Memorial Foundation for Neuro-Endocrine Research, and the Research Service of the Worcester State Hospital.

1 (a) Freeman, H., Rodnick, E. H., Shakow, D., and Lebeaux, T. The Carbohydrate Tolerance of Mentally Disturbed Soldiers, *Psychosom Med* **6** 311, 1944. (b) Robinson, G. W., Jr., and Shelton, P. Incidence and Interpretation of Diabetic-Like Dextrose Tolerance Curves in Nervous and Mental Patients, *J A M A* **114** 2279 (June 8) 1940. (c) Braceland, F. J., Meduna, L. J., and Vaichulis, J. A. Delayed Action of Insulin in Schizophrenia, *Am J Psychiat* **102** 108, 1945.

From the first 29 subjects tested by us the blood was withdrawn over a total period of two hours, according to the technic of Fraser, Albright and Smith.<sup>2</sup> Since the reaction in the second hour showed no abnormality, it was decided to restrict the study to the first hour in the rest of the series. The blood was analyzed for sugar by the Folin-Wu method (macroalkaline tartrate), with the actual reading made with the use of a photoelectric colorimeter.

## RESULTS

The results of the tests on the patients were compared with our own values for a series of 20 normal men (table 1). When the whole group of patients (93) is considered, it may be seen that during the course of the first hour the chief difference between the mentally disturbed patients and the normal group lay in the mean value for the thirty minute period. For the patients it was 41.4 mg per hundred cubic centimeters, as compared with 29.6 mg for the normal subjects. The difference of 11.8 mg between the mean level of the blood sugar for the patients and that for the normal subjects is statistically

TABLE 1—Means of Values for Blood Sugar During the Insulin Tolerance Test in 20 Normal Men and 93 Mentally Disturbed Soldiers

Type of Subject	Number	Blood Sugar, Mg per 100 Cc				
		Fasting Value	After Insulin			
			30 Min	60 Min	90 Min	120 Min
Normal	20	87.1	29.6	61.1	75.3	79.6
Psychiatric	93	87.1	41.4	65.3	68.2 *	75.8 *

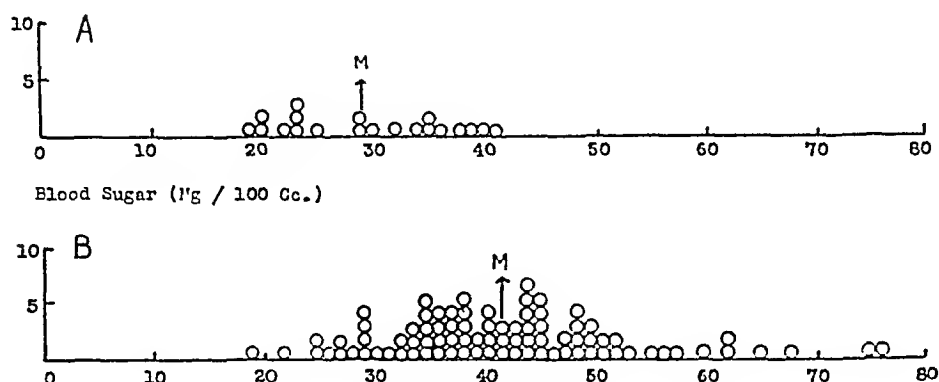
\* Observations on 29 subjects

significant, the probability of its occurring by chance being less than 1 in 100. The fasting values and those for the sixty minute period were not particularly dissimilar. This lesser degree of hypoglycemia in the patients indicates a resistance to the blood sugar—reducing effect of insulin, which is quite similar on the whole to that noted in the chronically ill schizophrenic group studied previously,<sup>3</sup> whose mean thirty minute level was 39.2 mg per hundred cubic centimeters. For 29 of the present patient subjects the values for the blood sugar were followed for two hours. In these patients it was found that the level of recovery was quite similar to that found in the normal subjects, as was true for the civilian schizophrenic subjects whose illness was prolonged. In

2 Fraser, R., Albright, F., and Smith, P. H. The Value of the Glucose Tolerance Test, the Insulin Tolerance Test and the Glucose-Insulin-Tolerance Test in the Diagnosis of Endocrinologic Disorders of Glucose Metabolism, *J. Clin. Endocrinol.* **1** 297, 1944.

3 Freeman, H., Looney, J. M., Hoskins, R. G., and Dyer, C. F. Results of Insulin and Epinephrine Tolerance Tests in Schizophrenic Patients and in Normal Subjects, *Arch. Neurol. & Psychiat.* **49** 195 (Feb.) 1943.

short, then, the outstanding defect in this group of patients was a failure to show a blood sugar-reducing effect, the secondary response, or rise in blood sugar, was normal



Frequency distributions of values for blood sugar thirty minutes after the injection of insulin in 20 normal men (A) and 93 mentally disturbed men (B). *M* (mean) for the normal subjects was  $29.6 \pm 1.64$  mg per hundred cubic centimeters, with a standard deviation of 7.4 mg. The mean for the psychiatric subjects was  $41.4 \pm 1.11$  mg per hundred cubic centimeters, with a standard deviation of 10.7 mg per hundred cubic centimeters.

Not all patients showed this insulin-resistant effect. The chart shows the distribution of values for the blood sugar for the thirty minute period in normal and in psychiatric subjects. The values for

TABLE 2—Means of Blood Sugar Values at Point of Maximum Hypoglycemia (Thirty Minutes After Administration of Insulin) in 20 Normal and 93 Mentally Disturbed Men Classified According to Diagnosis Groups

Type	Number	Blood Sugar, Mg per 100 Cc
Normal	20	29.6
All patients with psychoses	71	41.2
Schizophrenia	45	40.7
Manic depressive psychosis	5	43.6
Undiagnosed type	9	41.4
Other types	12	41.8
All nonpsychotic patients	22	42.7
Psychoneurosis	12	44.6
Psychopathic personality	7	40.0
Other disturbances	3	41.3

the normal subjects are distributed within a narrow zone between 19 and 41 mg per hundred cubic centimeters. For the patients, the values extend over a much broader range, from 19 to 76 mg per hundred cubic centimeters. Forty-three of the patients, or 46 per cent, had values for the blood sugar that were higher than the maximum reading

for any normal subject. This figure corresponds closely with that found in the chronic schizophrenic population (41 per cent) <sup>3</sup>

The patients were classified by diagnostic groups (table 2) based on the decisions of the research staff of the hospital. The majority (71) were found to be psychotic, the predominant disease being schizophrenia. Of the 22 nonpsychotic patients the larger number (12) were considered to be psychoneurotic. The lower reactivity to insulin was found to occur with approximately equal frequency in all diagnostic groups, so that there was no apparent relation to the type of mental disturbance.

Resistance to exogenous insulin is present in patients with schizophrenia <sup>4</sup> but is not restricted in psychotic states to that condition alone. It is a phenomenon widespread throughout all types of mental disturbance. In this sense it is similar to the frequent occurrence of decreased dextrose tolerance in persons who show various types of psychiatric abnormalities <sup>1a, b</sup> and is probably related to similar physiologic factors, although analysis shows no correlation between the two phenomena in individual subjects. It is of interest, also, that resistance to insulin was present in these patients, whose illness was of recent onset, to as great a degree as in the previous group of schizophrenic patients, whose average duration of illness was four years.

#### COMMENT

The physiologic background for this resistance to insulin is as yet not known. The main factors to be considered are the functional state of the liver and the activity of the endocrine glands. Production of insulin is probably adequate—otherwise one would expect abnormal fasting values. It may be delayed, as Braceland, Meduna and Vaichulis <sup>1c</sup> have shown because of the presence of anti-insulin factors. Of these factors, it does not seem likely that adrenomedullary activity is at fault because (a) the response to hypoglycemia (which calls forth sympathicomimetic substances) is essentially normal, and (b) the response of the blood sugar to injected epinephrine is less in schizophrenic patients than in normal persons <sup>3</sup>. Logically, therefore, one would not expect that in psychiatric subjects its anti-insulin effect would be greater.

Resistance to insulin is found in patients with clinical hyperpituitarism, hyperadrenalism and hypothyroidism <sup>2</sup>. Our patients <sup>5</sup> were characterized by low metabolic rates, a fact which, among others, suggests that the role of the thyroid may be an important one. Investigation is going on with respect to the other glands.

The effect of insulin resistance in psychiatric disturbances is as yet obscure. One cannot predicate from this investigation that the

<sup>4</sup> Braceland and associates <sup>1c</sup> Freeman and associates <sup>3</sup>

<sup>5</sup> Hoskins, R. G., and Freeman, H. Unpublished data



relative efficacy of endogenously produced insulin is lessened, but the assumption would be valid, both from the results of the present study and the observation of a decreased dextrose tolerance. In the final analysis, it would mean that glucose is not properly utilized, and from this point of view prolonged dysfunction may be a factor either in the activation or in the perpetuation of a mental disturbance, since the central nervous system is dependent on carbohydrate alone for its metabolic needs.

#### SUMMARY

A study of the sensitivity of the blood sugar response to injected insulin in a series of 20 normal men and of 93 mentally disturbed soldiers revealed that the mean maximum level of hypoglycemia (in thirty minutes) was 29.6 mg per hundred cubic centimeters in the former and 41.4 mg per hundred cubic centimeters in the latter. This difference in reactivity was statistically significant. Forty-six per cent of the patients showed a less pronounced drop in blood sugar than any of the normal subjects. The secondary rise in blood sugar following the hypoglycemia was the same in the two groups. This resistiveness to insulin was noted with all clinical types of mental disturbance and is probably indicative of a coincidental change in the reactivity of the endocrine factors controlling the regulation of blood sugar.

#### CONCLUSION

Acute episodes of mental disturbance, irrespective of diagnostic type, are characterized by resistance to the hypoglycemic effect of injected insulin.

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# HISTOPATHOLOGIC CHANGES IN CEREBRAL MALARIA AND THEIR RELATION TO PSYCHOTIC SEQUELS

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WORLD War II has again conferred outstanding importance on the problem of malaria. This illness, which more than any other was responsible for casualties in World War I, has played a tremendous role in the second conflict as well (Wales<sup>1</sup>). The neuropsychiatric complications of malaria are more common than are generally known and have been recognized since ancient times. Malarial psychoses were known even to Hippocrates and Galen. Chavigny,<sup>2</sup> Porot and Gutmann,<sup>3</sup> Hesnard<sup>4</sup> and others made extensive studies of the malarial psychoses and proposed various classifications of them. Pasmanik,<sup>5</sup> who studied more than 5,000 cases of malaria, noted mental disorders in 2 per cent of them. Forrester,<sup>6</sup> who studied this problem during the first world war, stated that malaria was the main cause of insanity among the Macedonian troops. In a monograph published in 1927, Anderson<sup>7</sup> dealt in detail with malarial psychoses and neuroses, paying special

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This study was aided by a grant from the American Foundation for Tropical Medicine

Dr Hans Meth, of Quito, Ecuador, provided the anatomic material, the clinical record and the necropsy reports of cases 1 and 2, and Dr Erwin Klein, of Guayaquil, Ecuador, provided the material and record on case 3. These physicians regret that, on account of the limited facilities available in the district where the patients resided, the laboratory work-up could not be as thorough as was desired.

1 Wales, H. G. Q. *Malaria and War in the Pacific*, Hygeia **21** 102 (Feb) 1943

2 Chavigny. *Complications nerveuses et mentales du paludisme*, Encephale **1** 387-391, 1912

3 Porot, A., and Gutmann, R. A. *Les psychoses du paludisme*, Paris med **22** 518-522 (Dec 29) 1917, **27** 241-248 (March 30) 1918

4 Hesnard. *Les psychoses palustres prolonguees*, Cong d med alienistes et de neurol de France, Tunis, April 1912, *Paludisme et, psychoses constitutionnelles*, Arch de med et pharm, November 1922, cited by Anderson<sup>7</sup>

5 Pasmanik, D. *Ueber Malaria psychosen*, Wien med Wchnschr **47** 518-519 (March 20) 1897

6 Forrester, A. T. W. *Malaria and Insanity*, Lancet **1** 16-17 (Jan 3) 1920

7 Anderson, W. K. *Malarial Psychoses and Neuroses. Their Medical, Sociological and Legal Aspects*, London, Oxford University Press, 1927

attention to the clinical and medicolegal aspects of the problem. In this country clinical reports were made by Masson<sup>8</sup> and Turner.<sup>9</sup> Brill and Pellicano<sup>10</sup> described a reversible organic psychosis in a case of malignant malaria in which the patient made a quick recovery with the early administration of quinacrine hydrochloride (atabine).

Neuropathologic investigations of cerebral malaria have also been carried out in conspicuous numbers. Classic is the work of Cerletti,<sup>11</sup> who paid special attention to the vascular changes. Bignami and Nazari<sup>12</sup> studied the punctiform hemorrhages frequently found in cases of cerebral malaria and interpreted them as due to diapedesis from collateral vessels. Durck<sup>13</sup> described nodules in the brain which he called "malaria granulomata." Marchiafava<sup>14</sup> classified the alterations in the central nervous system as intravascular, vascular and extravascular. Rigdon and Fletcher<sup>15</sup> studied the lesions occurring in the brain of a child who died in the acute stage of infection with *Plasmodium falciparum* and in the brains of monkeys, chicks and ducks infected with malaria. They found the lesions to be similar in human and in experimental cases and interpreted them as due to anoxemia. Several other studies, dealing with special aspects of this neuropathologic problem, have been carried out.

The purpose of this investigation is to reexamine this timely subject with the assistance of more modern neurohistologic methods, not used in previous researches. Furthermore, an attempt will be made to interpret the relation of these pathologic changes to the psychotic manifestations which at times complicate this illness.

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8 Masson, C. B. Effect of Malaria on the Nervous System with Special Reference to Malarial Psychoses, *Am J M Sc* **168** 334-371 (Sept.) 1924.

9 Turner, C. C. The Neurologic and Psychiatric Manifestations of Malaria, *South M J* **29** 578-586 (June) 1936.

10 Brill, N. Q., and Pellicano, V. L. Estivoautumnal Malaria with Frontal Lobe Syndrome, *J A M A* **121** 1150-1152 (April 3) 1943.

11 Cerletti, U. Die histopathologischen Veränderungen der Hirnrinde bei Malaria Perniciosa, in Nissl, F., and Alzheimer, A. *Histologische und histopathologische Arbeiten über die Grosshirnrinde*, Jena, Gustav Fischer, 1910, vol. 4 pp. 169-266.

12 Bignami, A., and Nazari, A. Sulle encefaliti emorragiche e sulla patogenesi delle emorragie malariche del cervello, *Riv sper di freniat* **42** 109-130, 1916.

13 Durck, H. Ueber die mit herdformigen Glaproduktionen einhergehenden Erkrankungen des Zentralnervensystems, *Arch f Schiffs- u Tropen-Hyg (supp)* **29** 43-76, 1925.

14 Marchiafava, E. Pernicious Malaria, *Am J Hyg* **13** 1-56 (Jan.) 1931.

15 Rigdon, R. H., and Fletcher, D. E. Lesions in the Brain Associated with Malaria. Pathologic Study on Man and on Experimental Animals, *Arch Neurol & Psychiat* **53** 191-198 (March) 1945.

## MATERIAL AND METHODS

Three cases of cerebral malaria due to *P. falciparum* were studied. One hemisphere of the brain in each of cases 1 and 3 was fixed in solution of formaldehyde U S P (1:10) and the other hemisphere in 80 per cent alcohol. The brain in case 2 was entirely fixed in solution of formaldehyde U S P.

Microscopic investigations were carried out with the following histologic methods: hematoxylin and eosin, for general study; the technics of Nissl for nerve cells, of Giemsa for parasites, of Bodian for neurofibrils, of Ramon y Cajal (Globus-Penfield modification) for astrocytes, of del Rio Hortega and Stern (Weil-Davenport modification) for microglia, of Weigert for elastic tissue and of Spielmeyer and Weil for myelin sheaths, sudan III, for fat, the Mallory and Van Gieson stain for connective tissue, and the Turnbull stain for iron. In addition, the following recently devised methods were used: the Eros stain for vascular pattern<sup>16</sup> and the Tomlinson and Grocott<sup>17</sup> stain for malarial parasites. Neumann's<sup>18</sup> modification of the Nissl method for material fixed in solution of formaldehyde U S P was used in case 2.

Sections stained with the Eros method for the vascular pattern were particularly useful because they permitted the study of the punctiform hemorrhages in the three spatial dimensions and allowed a differentiation of the erythrocytes, which appeared red, and the malarial pigment, which appeared black. No such differentiation would have been possible with the Pickworth benzidine method. The Tomlinson and Grocott method was successful in only a few sections. Many sections were treated with ammonium sulfide for removal of the malarial pigment, as suggested by Tomlinson and Grocott, but were later stained with ordinary methods.

In preparation of the material in case 1, frozen sections, 120 to 200 microns thick, were cut, dehydrated and mounted in balsam without being stained. With these preparations it was possible to study the distribution of the malarial pigment, which was of natural color. Inasmuch as the pigment was almost completely contained within the vessels, the course of the latter was well outlined. Thus, the angioarchitecture in this case could be studied in these sections.

For sake of brevity, only cases 1 and 2 will be reported here in detail. Case 3 was essentially similar to case 2, except that the lesions were less pronounced.

## REPORT OF CASES

**CASE 1—Clinical Summary**—The patient was found unconscious on a road which leads to the Ecuadorian region of the Amazon River, where malaria is endemic. He was a man apparently 20 to 22 years of age, of mixed white and Indian blood, but predominantly Indian. He was immediately taken to the hospital Eugenio Espejo, of Quito, Ecuador, where he arrived at 11 p. m. On admission, he was in a state of coma, from which he never aroused. The skin and the scleras were yellowish. The liver was enlarged, its lower border extending 4 cm. below

16 Eros, G. Method for Fuchsin Staining of the Network of Cerebral Blood Vessels, *Arch. Path.* **31**: 205-219 (March) 1941.

17 Tomlinson, W. J., and Grocott, R. G. A Simple Method of Staining Malaria Protozoa and Other Parasites in Paraffin Sections, *Am. J. Clin. Path.* **14**: 316-326 (June) 1944.

18 Neumann, M. A. A Rapid Method for the Differentiation of Nerve Cells in Old Formalin Fixed Material, *J. Neuropath. & Exper. Neurol.* **1**: 348-350 (July) 1942.

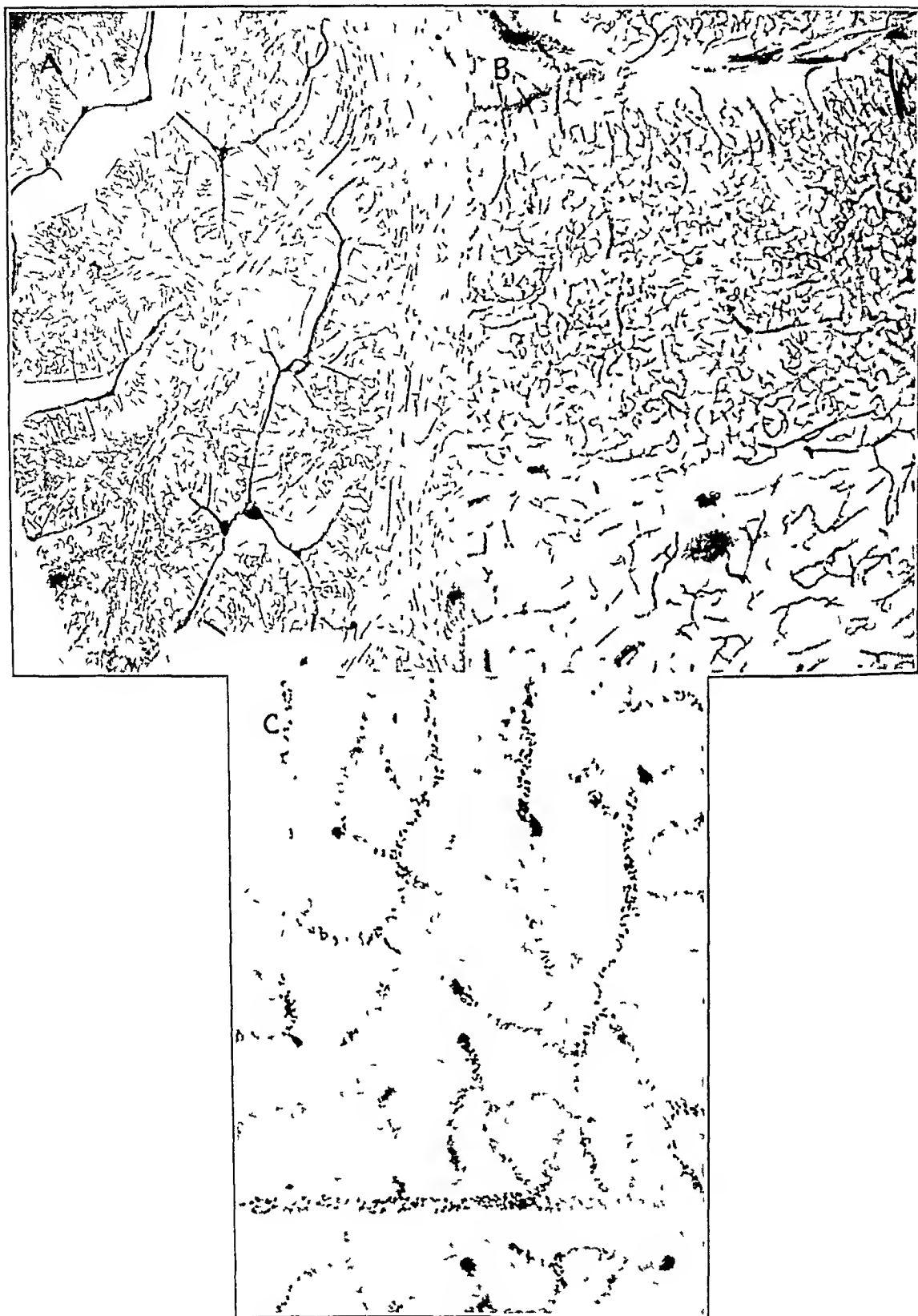


Figure 1

*(See legend on opposite page)*

the costal margin. The spleen could not be palpated. Smears of blood revealed trophozoites of the *P. falciparum* type. The patient died the following morning at 3 a. m. Unfortunately, no relative came to the hospital or could be reached by mail, so that no anamnestic data are available. However, on account of the condition in which the patient was found, it was felt that the illness had had an acute course.

*Necropsy*.—Autopsy was performed eleven hours after death. The bases of the lungs were congested and edematous. The liver was enlarged and friable. The cut surface appeared yellowish. The myocardium was flabby and yellow. The spleen was slightly enlarged. The kidneys were congested. The brain presented external hydrocephalus and diffuse edema. When the cerebral hemispheres were cut in transverse sections, numerous tiny hemorrhagic spots were noted.

*Microscopic Examination of the Brain*.—The histologic features presented by this case may be divided into four categories: changes involving (1) the blood vessels and their content and changes affecting (2) the nerve cells, (3) the glia and (4) the myelin sheaths.

The first category of changes was by far the most pronounced. Thick, unstained sections showed a tremendous amount of malarial pigment. Since this pigment was almost exclusively contained within the blood vessels, it beautifully outlined the whole cerebral and cerebellar angioarchitecture, which appeared in these unstained sections almost as distinctly as in sections prepared with stains specific for the vascular pattern or with injection methods (fig. 1). When the same sections were examined at higher magnification (fig. 1C), it was noted that the dots of pigment were almost uniformly diffused in the capillaries. However, at certain points the black dots appeared particularly condensed as though they would form small plugs. This was observed especially where branches were given off or where the vessels made a sharp curvature. In some areas it was also possible to recognize the presence of small hemorrhages, which appeared as gray areas surrounding capillaries (fig. 1B). These gray areas consisted of accumulated pigment, disclosing thus that even parasitized red cells could be extravasated into the nerve tissue.

In Eros sections it was possible to distinguish the two chief contents of the vessels, namely, the dots of pigment, which appeared black, and the erythrocytes, which stained red. Inasmuch as the malarial condition had caused an anemic state and the red cells were decreased in number and partially dehemoglobinized, the vessels did not appear as intensely red as in sections prepared from normal brains. The same sections disclosed the increased tortuosity of the vessels in the perivascular space and the presence of a large number of small hemorrhages. These

#### EXPLANATION OF PLATE

Fig. 1 (case 1).—Photomicrographs from unstained frozen sections, 120 to 200 microns thick. The malarial pigment, which is contained in the vessels, outlines the vascular pattern.

A (low magnification), cerebellar angioarchitecture. B (low magnification), section from a cerebral area, showing the difference in the vascular pattern in the cortex (upper part of the picture) and in the white matter (lower part). In the white matter it is possible to recognize a small hemorrhagic area, represented by a group of extravasated dots of pigment. C, section from a cortical area (medium magnification), revealing that the coloration is due to the granules of malarial pigment contained in the capillaries.

hemorrhages were particularly numerous in the subcortical white matter (fig 2), but occasionally they were encountered in the cortex itself. In the cerebellum they were by far more frequent in the molecular layer of the cortex. The cortical hemorrhages were generally ill defined and consisted of red cells extravasated by diapedesis (fig 3). In the white matter the hemorrhagic areas were generally

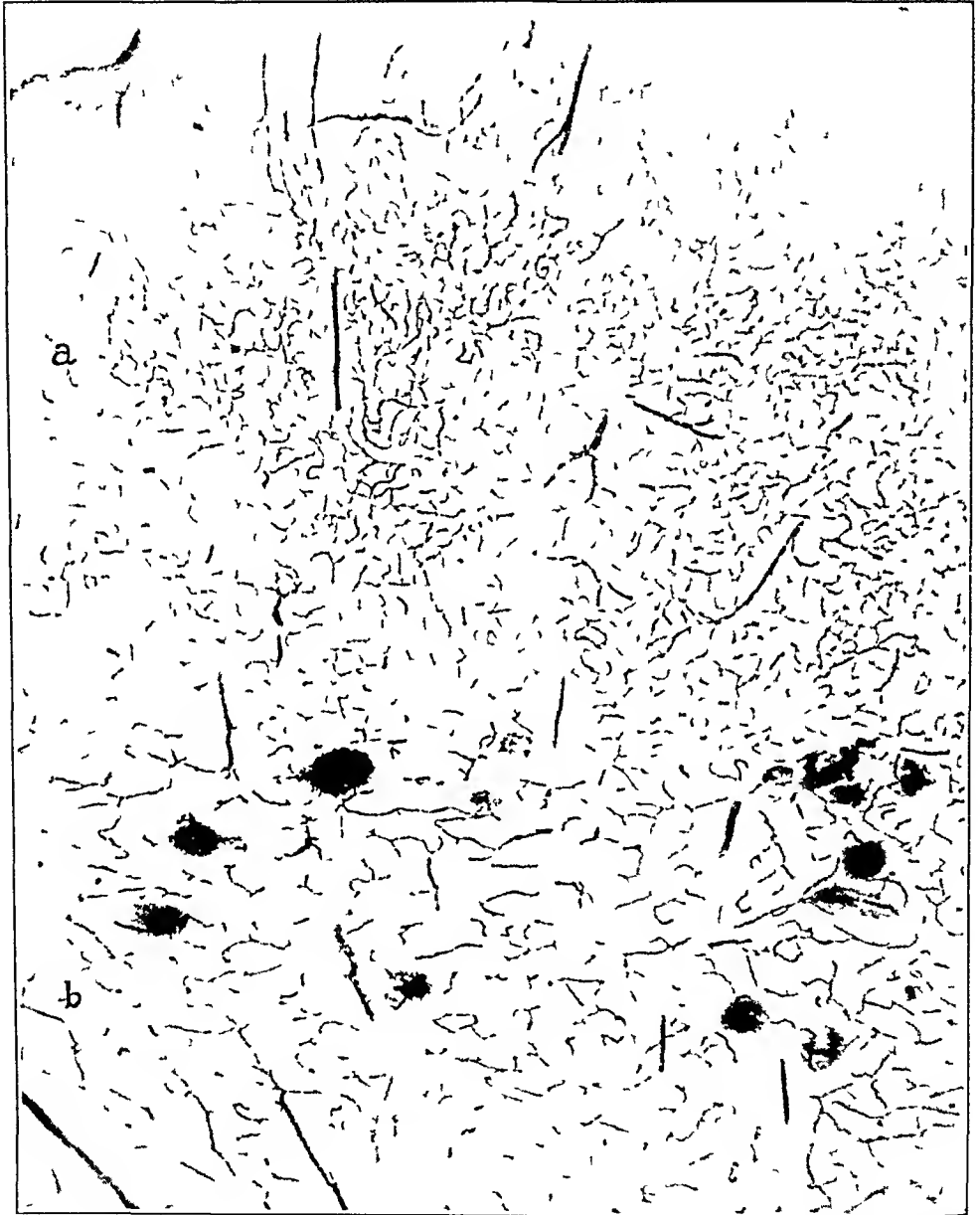


Fig 2 (case 1)—Small hemorrhages in the subcortical white matter. The upper part of the picture (a) shows the vascularization of the cortex, the lower part (b) that of the white matter. Eros method, low magnification.

roundish. In the center of many of them one could observe a capillary plugged with dots of pigment (fig 4 A and B). These dots obviously caused occlusion of many capillaries. In some instances the dots of pigment appeared so numerous

at the point of occlusion as to cause an enlargement and distention of the capillary (fig 4 *A*) In several instances the extravasated red cells surrounded closely the occluded vessel and were in immediate contact with its wall (fig 4 *A*) Oftener it was possible to distinguish around the capillaries a clearer central area, which contained fewer red cells, and a concentric peripheral area, where the red cells and the black dots were more numerous (fig 4 *B*) In still other cases the clearer area was almost entirely deprived of blood cells, which were located in the peripheral area (fig 4 *C* and fig 8 *A*) Since Eros sections visualized the capillaries in the three spatial dimensions, it was possible to rule out the possibility that the extravasated cells were coming from collateral capillaries surrounding the hemorrhagic

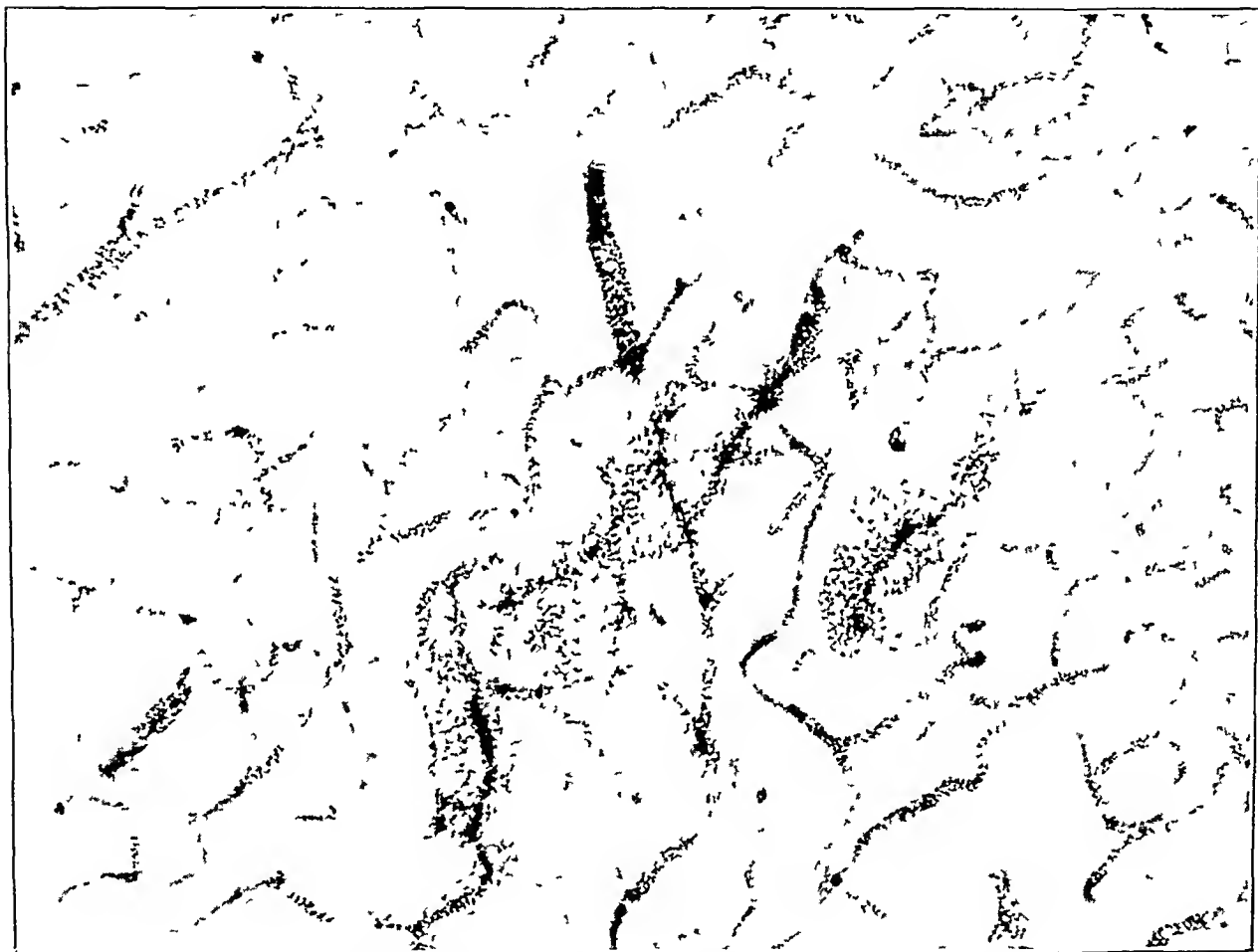


Fig 3 (case 1) —Diapedesis from cortical capillaries The dots of pigment may be distinguished from the red cells, which are less intensely and less distinctly stained Eros method, low magnification

area I could convince myself that in almost all instances the red cells had extravasated from the occluded central capillary, either above or below the point of occlusion No occlusion of medium or large vessels was seen in this case The Eros stain revealed that in the larger vessels of the meninges and of the brain the dots of pigment (and therefore the parasites) were located only at the periphery of the lumen, close to the vascular wall

Sections prepared with other methods confirmed the striking involvement of the vascular system observed in Eros preparations Sections stained with hematoxylin and eosin and with the Nissl method and examined with low magnifi-



cation revealed a notable increase in blood vessels. Such an increase in blood vessels, however, might probably be more apparent than real, since the blood vessels were better evidenced on account of their engorgement and the productive changes in their walls. The increase in blood vessels was also noted in the white matter, in addition to the hemorrhages already described and to perivascular necrotic foci, to be described later. The medium-sized vessels appeared more tortuous than usual and occasionally rotated on their axis, so that the secondary branches were twisted. The new formation of pockets of vessels, as described by Cerletti, could easily be detected in sections stained with the Mallory aniline blue method. One could see bundles of newly formed capillaries within a single perivascular space (fig 5 *B*). On examination with a high power lens the vessels showed interesting features both in their walls and in their lumen. The capillaries disclosed conspicuous proliferation of the endothelial cells. In the vessels in which the different coats were distinguishable both intimal and adventitial cells appeared stimulated to proliferation by the malarial infection. The new-formed endothelial cells of both meningeal and cerebral vessels were often seen projecting into the lumen. Often they were seen in the act of detaching or as already detached from the wall and entering the free circulation. Parasites were occasionally seen attached to the endothelial cells but never ingested by them. The adventitial cells presented changes involving the nucleus more than the cytoplasm. The nuclei were enlarged and rich in chromatin, often they were elongated or oval. At times the chromatin was gathered at the periphery of the nucleus in a ringlike distribution.

The majority of the red cells of the cerebral vessels appeared to be parasitized (fig 5 *A*), as revealed by the fact that they contained a dot of pigment at one extremity of the cytoplasm. Parasites were generally obscured by the pigment and could not be seen. However, a few sections, prepared with the Gomlinson-Grocott method, showed a few clear trophozoites. Other sections, stained with hematoxylin and eosin, after the pigment had been dissolved with ammonium sulfide, also showed some clear trophozoites. However, since each mass of pigment stands for a parasite, the gravity of the infection could be easily evaluated in this case. A few schizonts and crescents were also seen. Monocytes were likewise numerous in all sections examined and showed a great affinity for basic stains, no matter what method was used. The large meningeal vessels contained a larger number of parasitized monocytes but by far a smaller number of infected erythrocytes.

The cortical architecture was as a rule well preserved. The nerve cells presented diffuse changes. Many of them presented unduly well visualized processes. The most frequently encountered alterations consisted of transitional stages in the direction of the ischemic type of degeneration or of clearcut ischemic changes (fig 6). The acute swelling of Nissl could be studied well in the motor area, especially in Betz cells located near capillaries full of parasites (fig 7 *A* and *C*). These cells presented swelling of the cytoplasm and dissolution of Nissl bodies. Some cells exhibited swelling, central chromatolysis and dislocation of the nucleus, indicating a process of retrograde degeneration (fig 7 *B*). Severe types of degeneration and pyknotic changes were not encountered. The cellular alterations described were accompanied with a mild increase in satellitosis.

Changes in the glia and the myelin sheaths were noted in connection with small necrotizing foci, especially in the subcortical white matter. These foci surrounded capillaries and appeared to coincide in their distribution, extension and architecture with areas in which small hemorrhages had presumably taken place.

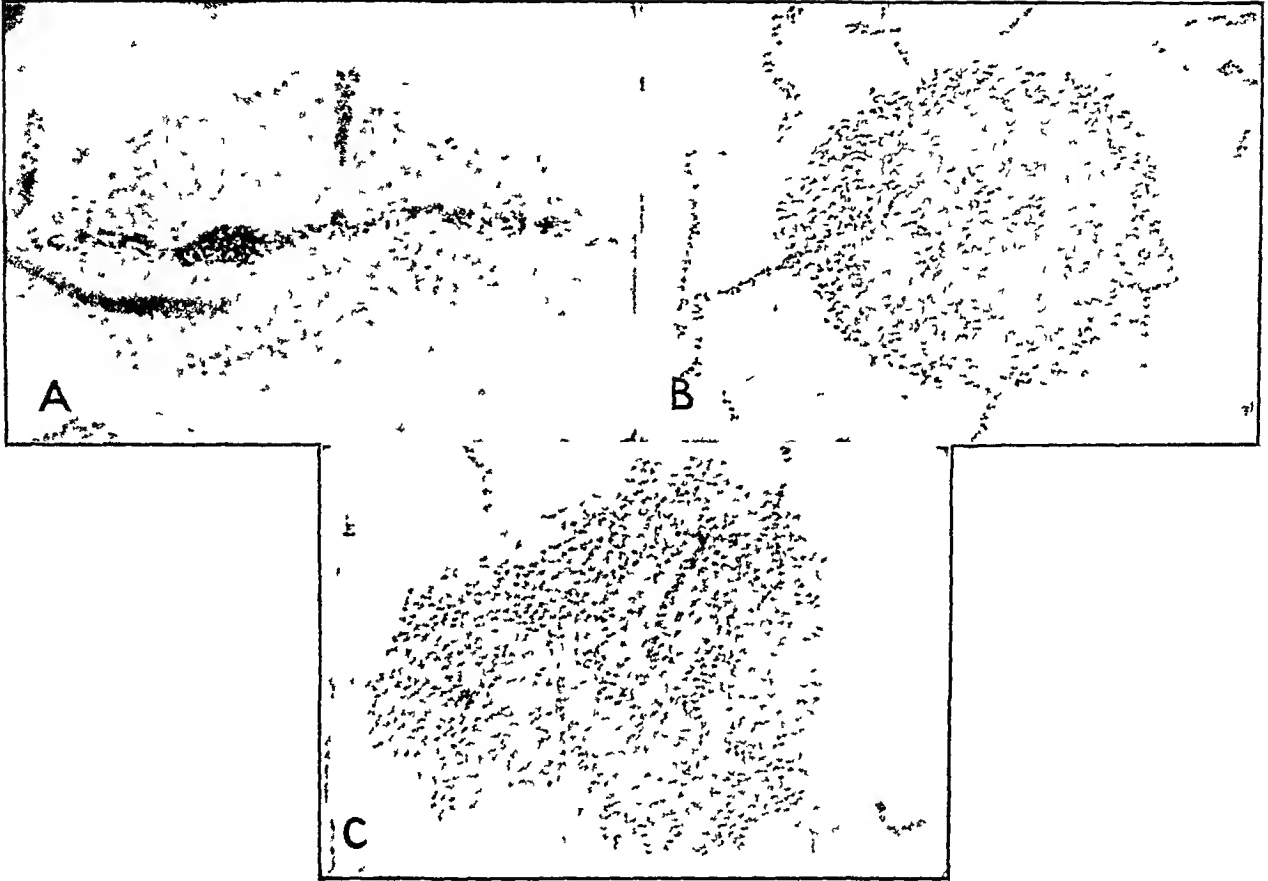


Fig 4 (case 1)—Color photomicrographs (Eros method, high magnification)

*A*, small hemorrhage, in the center of which is a capillary, loaded with parasites. At the point of occlusion the large amount of pigment distends the capillary. *B*, small hemorrhage crossed by a capillary occluded with a plug of malarial pigment. The point of occlusion is centrally located and is clearly visible. In the central area rarefaction of the red cells has begun. *C*, two small hemorrhages, in the central area of which the red cells have almost entirely disappeared.



In the center of them it was generally possible to recognize a capillary loaded with parasites (fig 8 *B*). The capillary was surrounded by an area of demyelination, as revealed by the Spielmeyer and Weil stain. A concentric peripheral area was also observed, in which at times red cells, but more often glia nuclei, were gathered. When these glia nuclei were present, formations similar to granu-

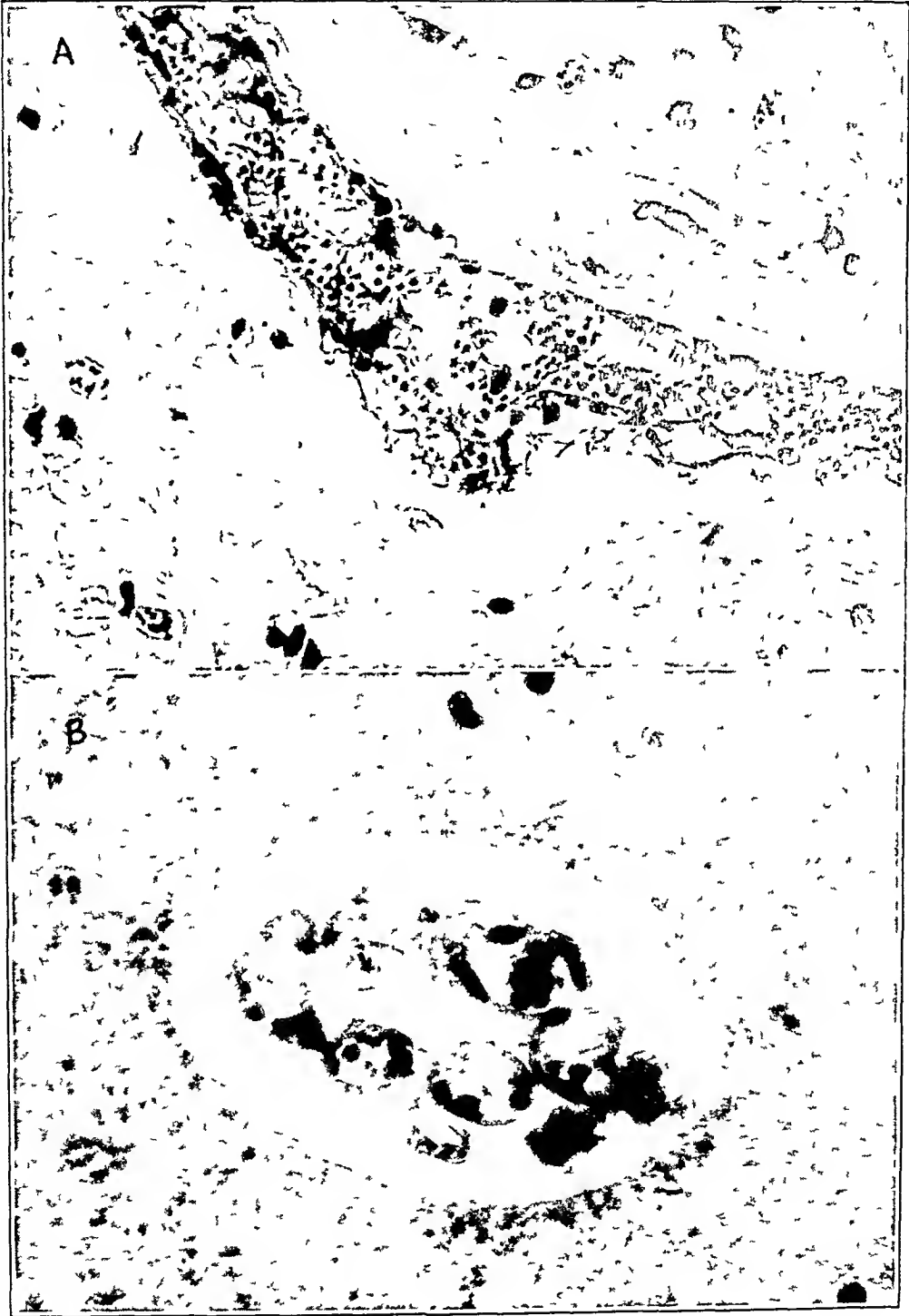


Fig 5 (case 1) —*A*, cerebral vessel loaded with malarial parasites and pigment. Notice also the enlarged perivascular space. Giemsa stain, medium magnification. *B*, pocket of newly formed capillaries within a single perivascular space. Mallory stain, high magnification.

lomas were observed (fig 8C). The white matter appeared altered, not only on account of the presence of these pseudogranulomas, in varying stages of formation, but also because the tissue was extremely edematous and loose.

Stains specific for glia did not reveal changes in addition to those described in relation to the pseudogranulomas. Sections stained with prussian blue did not disclose an abnormal amount of iron.

No hemorrhages, demyelinating areas or pseudogranulomas were noted in the brain stem or in the three upper cervical segments, which were the only part of the spinal cord available for study.

CASE 2—*Clinical Summary*—G. M., a 6 year old orphan child, of mixed white and Indian blood, was taken to the Milagro Hospital by his neighbors. They had



Fig 6 (case 1) —Ischemic changes in nerve cells. Nissl stain, medium magnification.

found him in convulsions and lying on the ground in a street of the town. They stated that for several days prior to his admission the child had had fever and had undergone convulsive seizures.

The patient entered the hospital on May 2, 1942 at 2:30 p. m. On admission he was noted to be in a state of malnutrition and presented a rachitic rosary. He was unconscious. His temperature was 40.6 C (105.1 F). Examination of the lungs revealed rales in the upper and middle portion. The abdomen was tympanic. The spleen could be palpated 5 cm. below the costal margin and was hard in consistency. The liver also could be palpated 2.5 cm. below the costal margin. The tendon reflexes were increased. The Babinski sign was elicited on both sides but not

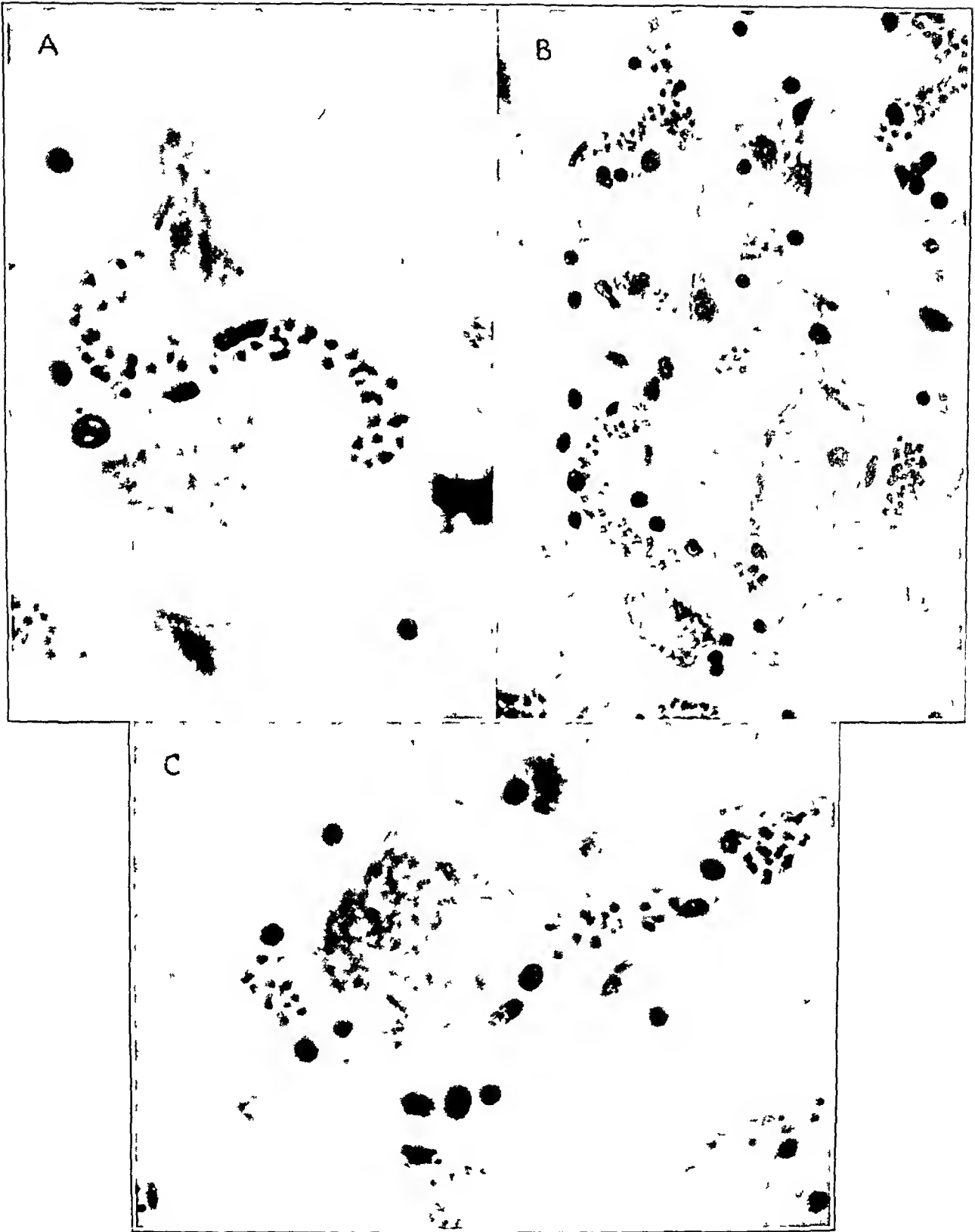


Fig 7 (case 1) — *A*, Betz cell, surrounded by a capillary loaded with parasites. Notice the dissolution of tigroid substance in the cytoplasm of the nerve cell. *B*, Betz cells, showing retrograde (axonal) degeneration. The nucleus is displaced, and the tigroid substance is dissolved in the center of the cell but preserved at the periphery. Notice also the large number of parasites in the neighboring capillaries. *C*, ganglion cell of the motor area, showing acute swelling. Nissl stain, high magnification.



Figure 8  
(See legend on opposite page)

consistently The patient underwent convulsive seizures approximately every thirty minutes, without acquiring consciousness in the intervals Examination of the blood could not be made The child died at 4 30 p m on the day of admission

*Necropsy*—Autopsy was performed one and a half hours after death The bases of the lungs and the abdominal organs were congested The liver and the spleen were considerably enlarged The spleen was dark and of hard consistency, and its capsule was distended When the skull was opened external hydrocephalus was noted The leptomeninges were slightly clouded The meningeal and the cerebral blood vessels were dilated and congested

*Microscopic Examination of the Brain*—The histologic alterations in this case were by far less pronounced than in the previous one Nevertheless, it was possible to recognize in every section studied diffuse and conspicuous involvement of the blood vessels The capillaries were increased in number, both in the white and in the gray matter Pockets of new-formed capillaries were often observed, especially in sections prepared with the Mallory aniline blue method All the vessels appeared dilated and congested Many of them were tortuous and were surrounded by an enlarged perivascular space In almost all capillaries the presence of parasites, with their granules of pigment, was noted However, the parasites were by far less numerous than in the previous case, so that in thick, unstained sections, prepared as previously described, the vascularization could not be visualized The endothelial changes were similar to those in the previous case and in many regions were even more pronounced Both meningeal and cerebral vessels exhibited conspicuous proliferation of endothelial cells, which became detached from the intima and entered the free circulation (fig 9 *A* and *B*) The adventitial cells also showed conspicuous stimulation They were increased in size and presented a large and hyperchromatic nucleus No hemorrhages were noted in this case Sections stained with the Eros method disclosed clots of nonparasitized red cells within the capillaries (fig 10) It seemed as though the erythrocytes would easily agglutinate within the vessels There was no extravasation of cells, however, around these clots or damage of the myelin sheaths, though the blood supply was diminished, as revealed by the fact that the surrounding vessels appeared slightly less impregnated with the Eros stain

The cortical architecture was well preserved throughout The nerve cells exhibited diffuse changes Many of them presented disintegration of Nissl bodies and unduly well visualized and tortuous processes In many instances typical ischemic changes were observed

Glial reaction was evident throughout Both the gray and the white matter exhibited an increase in glia nuclei Such increase, however, was particularly evident around the capillaries of the white matter (fig 11 *A*) Enlarged nuclei

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#### EXPLANATION OF PLATE

Fig 8 (case 1) —Formation of a pseudogranuloma (*A*) In a small subcortical hemorrhage, the red cells have almost completely disappeared from the center of the area (only a few are left in radial positions) but are still numerous at the periphery Mallory stain, medium magnification (*B*) The red cells have disappeared from the peripheral area also This area appears edematous and of loose consistency and shows proliferation of glia cells Note also a central capillary loaded with parasites Giemsa stain, medium magnification (*C*) The pseudogranuloma is now almost formed At the center one sees in cross section a capillary loaded with parasites A necrotic central area is surrounded by a peripheral cuffing consisting predominantly of glia cells Nissl stain, medium magnification



and ameboid elements were frequently encountered, especially in the sixth layer of the cortex and in the subcortical white matter. Cajal sections showed hyperplasia and hypertrophy of the astrocytes. A single astrocyte exhibited at times



Fig 9 (case 2) —Sections stained with hematoxylin and eosin

*A*, (low magnification), meningeal artery, showing pronounced desquamation of endothelial cells from the intima

*B*, (high magnification), detail from *A*. Here, *ad* indicates adventitia, *m*, media, *i*, intima, with well differentiated elastica, *end* endothelial cells becoming detached from the intima and entering the free circulation, and *bl*, clotted blood

several vascular feet, which reached various capillaries (fig 11 *B*) No pseudo-granulomas or areas of demyelination were noted in the white matter

#### COMMENT

The punctiform hemorrhages, as described in case 1, and the histologic processes which they subsequently undergo are perhaps the outstanding features of cerebral malaria The dependence of these hemorrhagic areas on the vascular pattern could be easily established in case 1 In fact, they were found almost exclusively in the molecular layer of the cerebellum and in the white matter of the brain, especially in the subcortical areas Pfeifer,<sup>19</sup> Cobb<sup>20</sup> and others, who have studied

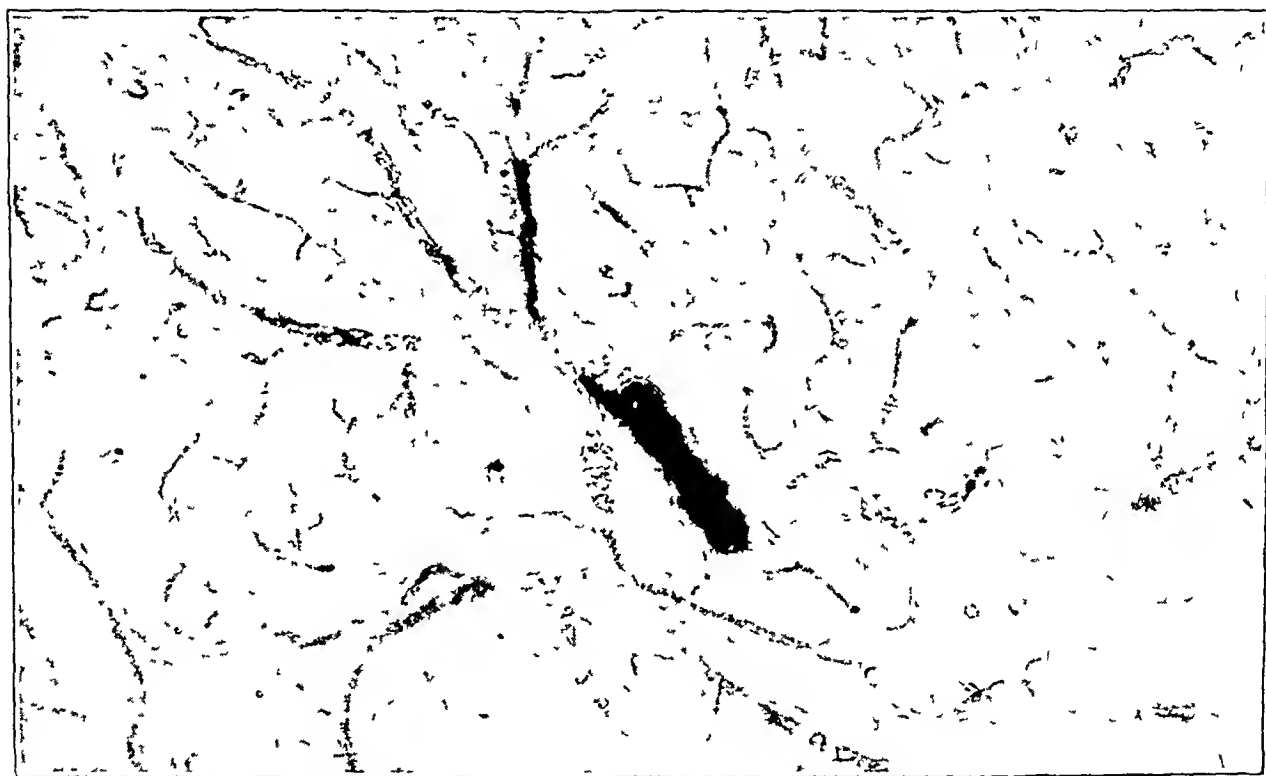


Fig 10 (case 2) —Clumping of red cells in cortical capillaries Note a few granules of malarial pigment in several vessels

the angioarchitecture of the nervous system with injection methods, have reported that the vascularization of the molecular layer of the cerebellum is much poorer than that of the granular layer and that the same is true of the vascularization of the cerebral white matter as compared with that of the gray matter When a blood vessel of a

19 Pfeifer, R A Die Angioarchitektonik der Grosshirnrinde, Berlin, Julius Springer, 1928

20 Cobb, S The Cerebrospinal Blood Vessels, in Penfield, W Cytology and Cellular Pathology of the Nervous System, New York, Paul B Hoeber, Inc, 1932, vol 2

poorly supplied area is occluded, collateral circulation cannot always be established. Therefore the vascular walls near the point of occlusion may undergo changes which will permit diapedesis, and the tissue supplied by the occluded vessel may undergo degenerative changes

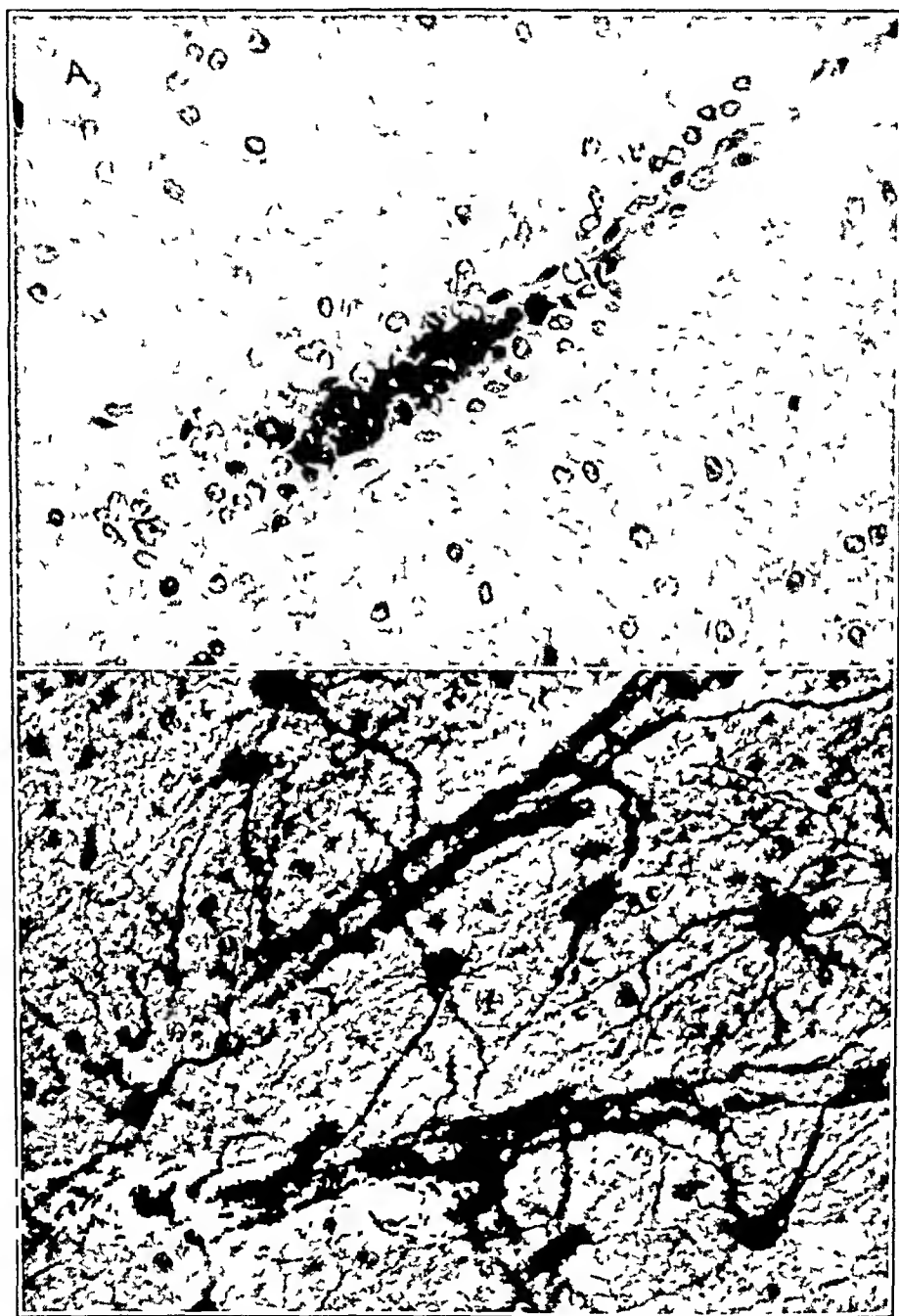


Fig 11 (case 2)—*A*, increased number of glia nuclei around a blood vessel. Hematoxylin and eosin, medium magnification. *B*, hypertrophy and hyperplasia of macroglia cells. Astrocytes send expansions to more than one vessel. Cajal stain (Globus modification), medium magnification.

In case 1, as well as in others reported in the literature, the hemorrhagic lesions were predominantly observed in poorly supplied regions, which were near the point of transition into richly supplied areas. The occlusions mentioned were due to plugs of granules of pigment, parasitized erythrocytes and newly formed endothelial cells. These plugs acted as real emboli and determined embolic lesions. The punctiform hemorrhages were generally seen around occluded capillaries. In a few instances complete occlusion could not be found, but the quantity of pigment was probably sufficient to slow the circulation and to produce alterations of the vascular walls to such a degree as to permit diapedesis. The hemorrhages consisted of a roundish cuffing of extravasated red cells. In sections stained with the Eros method and in thick, unstained sections it was possible to recognize that several of the extravasated red cells contained granules of pigment and were therefore parasitized. This is important because Bignami and Nazari<sup>12</sup> claimed that parasitized red cells never extravasate, presumably because their motility is impaired.

The hemorrhages were of two types. The first type consisted of red cells, which surrounded closely the capillary. In the second type the capillary was surrounded by a pale area in which no, or very few red cells were present. Sections stained with the Spielmeyer and Weil method disclosed that the pale area was undergoing demyelination. I have observed all gradations between the first and the second type of hemorrhages, and I am under the impression that the second type represents a more advanced stage. The red cells start to undergo rarefaction in the demyelinating area, from which they finally disappear, and are left only in the peripheral area. I feel that the red cells in the central area disintegrate gradually because in a subsequent stage they disappear also from the peripheral area and are replaced with glia cells. When these glia cells gather in the peripheral area, one sees those features which Durck<sup>13</sup> called malarial granulomas. These foci consist of a central blood vessel surrounded by a demyelinating area, which is, in turn, surrounded by an area of gliosis. From the foregoing description it is obvious that these lesions are the result of the hemorrhages and that the glial proliferation is a reparative reaction to the local damage. No inflammatory changes are noted. It seems incorrect, therefore, to call these nodules granulomas, as it would be to designate the so-called Lichtheim plaque of pernicious anemia as a granuloma. However, if one wishes to emphasize the apparent similarity of these nodules to granulomas, one might call them "malarial pseudogranulomas."

Bignami and Nazari and others maintained that the hemorrhagic lesions are small infarcts and that the hemorrhagic red cells have

extravasated from collateral capillaries, located in the vicinity of the occluded vessel. Such is, in reality, the impression which one gets in studying sections prepared with the usual methods. However, if one uses thick sections which permit visualization of the capillaries in the three spatial dimensions one easily recognizes that the extravasated red cells do not come from neighboring capillaries but come only from the central vessel. A process of diapedesis occurs above and below the point of occlusion or partial occlusion. The absence of red cells in the pale area surrounding the capillary is explained by the fact that the erythrocytes have disappeared in this area which is undergoing demyelination and at times necrosis. Often the occluded vessel has a tortuous course within the necrotic focus, so that one may receive the impression that another capillary is undergoing a process of diapedesis. In a few instances several neighboring capillaries presented diapedesis because they were all occluded. No occlusion of precapillaries or of medium or large vessels was observed.

These perivascular lesions caused by embolic plugs remind one of the experimental and other pathologic studies carried out by Putnam and his school<sup>21</sup> in an attempt to explain the pathogenic mechanism of multiple sclerosis. The lesions described in the present report undoubtedly demonstrate that plugs occluding capillaries may cause demyelinating areas and to a certain extent corroborate Putnam's theory. The fact that the lesions occur predominantly in the subcortical white matter is also a characteristic common to many cases of multiple sclerosis and may indicate that in the latter disease also the location of the lesions is determined by the vascular pattern. These demyelinating areas, however, differ in the two conditions inasmuch as perivascular infiltrations of lymphocytes, which are often found in cases of multiple sclerosis and which may be considered as the expression of an allergic (Ferraro<sup>22</sup>) or an inflammatory reaction, are absent in cerebral malaria. In addition the perivascular pathologic process in malaria more often than in multiple sclerosis goes beyond a state of demyelination to complete focal necrosis with little glial reparative reaction. Further-

21 Putnam, T. J., McKenna, J. B., and Morrison, L. R. Studies in Multiple Sclerosis. I. The Histogenesis of Experimental Sclerotic Plaques and Their Relation to Multiple Sclerosis, *J. A. M. A.* **97** 1591-1596 (Nov. 28) 1931. Putnam, T. J. The Pathogenesis of Multiple Sclerosis. A Possible Vascular Factor, *New England J. Med.* **209** 786-790 (Oct. 19) 1933. Lesions of "Encephalomyelitis" and Multiple Sclerosis. Venous Thrombosis as the Primary Alteration, *J. A. M. A.* **108** 1477-1480 (May 1) 1937. Hoefer, P. F. A., Putnam, T. J., and Gray, M. G. Experimental "Encephalitis" Produced by Intravenous Injection of Various Coagulants, *Arch. Neurol. & Psychiat.* **39** 799-812 (April) 1938.

22 Ferraro, A. Pathology of Demyelinating Diseases as an Allergic Reaction of the Brain, *Arch. Neurol. & Psychiat.* **52** 443-483 (Dec.) 1944.

more, in reviewing the literature on malaria, one is struck with the relative scarcity of pathologic reports on the spinal cord. This may be due, however, to the fact that serial studies of the spinal cord have never, to my knowledge, been carried out in cases of malaria. Small foci along the long tracts of the spinal cord may give rise to obvious clinical symptoms and yet may remain unnoticed if serial sections are not made. As a matter of fact, many authors have reported clinically the occurrence in the course of malaria of syndromes resembling multiple sclerosis (Torti and Angelini,<sup>23</sup> Canellis,<sup>24</sup> Triantaphyllides,<sup>25</sup> Papastrategakis,<sup>26</sup> and Parrot<sup>27</sup>). In the American literature, Spiller<sup>28</sup> reported 1 such case, both from a clinical and a pathologic point of view. All the foregoing observations seem to indicate that embolic plugs, similar to those encountered in cerebral malaria, may constitute a factor in the mechanism of multiple sclerosis.<sup>29</sup>

In case 2 no actual thrombi or emboli were observed. However, Erios sections revealed many intravascular clumpings of nonparasitized red cells (fig. 10). Some capillaries were filled with cylinders of tightly packed cells. Knisely and associates<sup>30</sup> observed the same phenomenon in cinematographic studies on monkeys infected with *Plasmodium knowlesi*. These plugs, or clumpings, were probably caused by the increased viscosity of the red cells, reported to occur in the course of malaria by numerous authors, and presumably did not arrest the circulation. In fact, no hemorrhages, necrotic foci or pseudogranulomas were noticed in this case. These clumpings of red cells, however, may cause a transitory state of ischemia, which, in turn, may

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23 Torti, A., and Angelini, A. Infezione malarica cronica coi sintomi della sclerosi a placche, *Riforma med* **12** 817-825 (June) 1891.

24 Canellis, S. Étude sur un cas de sclerose en plaques disseminees a la suite d'une intoxication par le miasme paludeen, *Gaz hebdomadaire de med* **24** 554-555 (Aug 26) 1887.

25 Triantaphyllides. Pseudo-sclerose en plaques d'origine palustre, *Arch de neurol* **26** 232-234 (Sept) 1893.

26 Papastrategakis, C., cited by Anderson.<sup>7</sup>

27 Parrot, L. M. Note sur un cas de sclerose en plaques d'origine paludenne, *Rev de med et d'hyg trop* **6** 98-101, 1909.

28 Spiller, W. G. A Case of Malaria Presenting the Symptoms of Disseminated Sclerosis, with Necropsy, *Am J M Sc* **120** 629-647 (Dec) 1900.

29 This problem will be discussed more thoroughly in further contributions, in which the neuropathology of malignant malaria will be studied as an aid to explain the pathogenic mechanisms of other neurologic conditions of possible vascular origin.

30 Knisely, M. H., Stratman-Thomas, W. K., and Eliot, T. S. Observations on Circulating Blood in the Small Vessels of Internal Organs in Living Macacus Rhesus Infected with Malarial Parasites, abstracted, *Anat Rec (supp)* **79** 90 (March) 1941.

be one of the factors responsible for the ischemic changes in the nerve cells

No special consideration will be given in this investigation to the nature of the malarial pigment. The reader is referred to the studies of Morrison and Anderson.<sup>31</sup> It will be mentioned only that, in agreement with the observations of these authors, it seems from the present investigation that in the nervous system too, the pigment is a morbid agent not because of its chemical qualities but because of its mechanical effect inasmuch as it causes vascular occlusions or slowing of the circulation.

Mesodermal changes were present in marked degree in all cases, thus disclosing that they are an important feature of cerebral malaria irrespective of the intensity of the illness. The adventitial cells of the meningeal and cerebral vessels were enlarged; the nuclei were rich in chromatin and had an increased affinity for basic stains. The endothelium lining the lumen of the vessels was also conspicuously stimulated. The endothelial cells were seen to be desquamating in large quantity and entering the free circulation. This phenomenon was observed not exclusively in capillaries, as reported by Bruchsch,<sup>32</sup> but also in large vessels. Many authors have attributed phagocytic activities to these endothelial cells (Barker,<sup>33</sup> Gaskell and Millar,<sup>34</sup> Seyfarth,<sup>35</sup> Thomson and Annecke,<sup>36</sup> Torrioli,<sup>37</sup>). On the other hand, Jaffe<sup>18</sup> reported that

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31 Morrison, D. B. and Anderson, W. A. D. The Pigment of the Malaria Parasite, *Pub. Health Rep.* **57** 90-94 (Jan. 16) 1942, On the Role of Parasite Pigment in the Malaria Parasitism, *ibid.* **57** 161-174 (Jan. 30) 1942. Anderson, W. A. D. Morrison, D. B., and Williams, E. F., Jr. Pathologic Changes Following Injections of Ferrihemate (Hematin) in Dogs. *Arch. Path.* **33** 589-602 (May) 1942. Anderson, W. A. D., and Morrison, D. B. Role of Parasite Pigment (Ferrihemic Acid) in the Production of Lesions in Malaria, *ibid.* **33** 677-686 (May) 1942.

32 Bruchsch, W. L. The Histopathology of Therapeutic (Tertian) Malaria. *Am. J. Psychiat.* **12** 19-65 (July) 1932. Activation of the Mesenchyme with Therapeutic Malaria, *J. Nerv. & Ment. Dis.* **76** 209-219 (Sept.) 1932.

33 Barker, L. F. A Study of Some Fatal Cases of Malaria, *Johns Hopkins Hosp. Rep.* **5** 219-277, 1895.

34 Gaskell, J. F., and Millar, W. L. Malignant Malaria in Macedonia, *Quart. J. Med.* **13** 387-426 (July) 1920.

35 Seyfarth, C. Die Malaria, in Henke, F., and Lubarsch, O. *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1926, vol. 1, pp. 178-248.

36 Thomson, J. G., and Annecke, S. Observations on the Pathology of the Central Nervous System in Malignant Tertian Malaria, with Remarks on Certain Clinical Phenomena, *J. Trop. Med.* **29** 343-346 (Oct. 15) 1926.

37 Torrioli, M. La fagoцитosis nella malaria, *Riv. di malariol.* **10** 321-347 (May-June) 1931.

granules of pigment are attached to, but not incorporated by, endothelial cells. Taliaferro and Mulligan,<sup>39</sup> in a particularly thorough study of the brains of rhesus monkeys during the terminal stage of infection with *P. knowlesi*, observed that phagocytosis by vascular endothelial cells was negligible as compared with that occurring in the spleen, liver and bone marrow. In this study, which was limited to the brain, I also observed that phagocytosis by endothelial cells was practically absent. The few instances in which it seemed to have occurred were equivocal. These observations, though not establishing a phagocytic action, do not disprove that these desquamated cells have a defensive action. It will be recalled here that Bietsch<sup>32</sup> attributed to this endothelial desquamation the therapeutic action of malaria in dementia paralytica. He expressed the belief that the tremendous stimulation of endothelial cells first increases and subsequently decreases the permeability of the cerebral capillaries.

The nerve cells presented with special frequency three types of changes. The most common consisted of gradual alterations in the direction of the ischemic type of change. They were obviously due to the ischemia produced by the vascular occlusions and to the secondary anemia. Second in frequency was the acute swelling of Nissl. Third was the retrograde cell change, possibly due to interruption of the axons in the white matter. This last change was observed only in case 1, which was the only one in my series to present necrotic foci.

In case 2, glial hypertrophy and hyperplasia were conspicuous and widespread. Ameboid elements were frequently observed in the sixth layer of the cortex and in the subcortical white matter. As already described by Duick,<sup>13</sup> conspicuous gathering of glia with nuclei was observed along the course of capillaries. These glial nuclei often formed a cuffing in a one cell layer for a long tract of the vessel. The changes of the glia described were by no means specific but might be interpreted in this case as a reaction to a deficient blood supply. The edema observed to a striking degree in all 3 brains must also receive particular attention.

If now one reconsiders the changes already described it is possible to draw some general conclusions. First, however, it must be recalled that the 3 cases studied in this investigation presumably represented an acute type of malaria. If the course in these cases had been longer,

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38 Jaffe, R. H. The Reticulo-Endothelial System. Its Role in Pathologic Conditions in Man, *Arch. Path.* 4: 45-91 (July) 1927, cited by Taliaferro and Mulligan.<sup>39</sup>

39 Taliaferro, W. H., and Mulligan, H. W. The Histopathology of Malaria with Special Reference to the Function and Origin of the Macrophages in Defence, *Indian Medical Research Memoirs*, no. 29, Calcutta, Thacker, Spink & Co., 1937, pp. 1-138.



additional alterations would undoubtedly have been observed. Some of the alterations here described seem to be reversible and compatible with clinical recovery following disappearance of the parasites and of the vascular blockages. Other alterations, on the contrary, especially some of those described in case 1, appear irreversible and may explain why even after a clinical recovery, the patient may remain "a changed man" (Wilson<sup>40</sup>). One may also state that though malaria is due to a minor parasitic infection the histologic reaction in the brain is not inflammatory. The infection does respect as a rule the hematoencephalic barrier. The comparatively few parasites which are extravasated into the nerve tissue promptly perish. The majority of the extravascular lesions are caused by physical mechanisms (vascular occlusion and slowing down of the circulation).

Of course, not all the lesions have to be attributed to these mechanisms. Two other important factors play roles which cannot be overlooked: first, the intermittent hyperthermic state, and second, the catabolic substances produced in the course of the illness. In experimental hyperthermia in fact, both parenchymatous and interstitial changes have been found (Hassin<sup>41</sup>). Acute cell disease of Nissl has been described in rabbits in which the temperature was raised to 44 C (111.2 F). In cases of hyperthermia of longer duration hyperemia of blood vessels, swelling of endothelial cells and hemorrhages were also observed by Omorokow<sup>42</sup>. Though in malaria the temperature does not rise over 107 F the hyperthermic state may have played a secondary role in the pathologic process in my cases. More difficult is it to determine the role played by the catabolic substances. Omorokow said it was possible that the lesions observed in his experimental cases might have been produced by the catabolic changes resulting from the hyperthermia.

What is the correlation between the cerebral changes described and the psychotic syndromes which sometimes complicate malaria or follow this illness even after apparent recovery? The literature on the psychotic complications of malaria is difficult to review on account of the different terminologies used in the various countries where the investigations were made. However, it seems to me that the most common psychotic conditions which have been described may be classified under four heads: (1) acute deliriums, (2) paranoid syn-

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40 Wilson, S. A. K. *Neurology*, edited by A. N. Bruce, Baltimore, Williams & Wilkins Company, 1940, vol. 1.

41 Hassin, G. B. *Histopathology of the Peripheral and Central Nervous Systems*, Baltimore, William Wood & Company, 1933.

42 Omorokow, L. Ueber den Einfluss hoher Temperaturen auf das Zentralnervensystem des Kaninchens, in Nissl, F., and Alzheimer, A. *Histologische und histopathologischen Arbeiten über die Grosshirnrinde*, Jena, Gustav Fischer, 1913-1914, vol. 6, pp. 1-32, cited by Hassin<sup>41</sup>.

dioms, (3) typical psychoses, such as schizophrenia and manic-depressive psychoses, and (4) organic conditions

The acute deliriums include conditions which have been designated by Anderson as "confusional psychoses" and which may terminate in "malarial coma." These deliriums are fundamentally similar to all the toxic-infective deliriums. They are distinguished, however, by their greater severity, by the more marked state of amnesia which they cause and by their frequent termination in a state of coma. Other differential characteristics are (1) periodicity of the symptoms in accordance with the febrile cycles and the sporulation of parasites, (2) possible epileptiform convulsions and other neurologic symptoms, and, finally (3) a tendency to fall into a state of agitated melancholia.

The cases reported in this article do not offer many clinical details for study, but their histologic alterations may help to explain the symptoms in other cases. These cases, especially case 1, reveal that the malarial delirium should not be interpreted merely as a complication of a general illness, similar to the other organic-infective deliriums. Its severity may be attributed directly to the pathologic process in the brain, even if it is not as marked or as acute as that in case 1 (edema of the brain tissue, diminished blood supply, complete anemia of certain areas). The irritation of the nerve cells caused by neighboring plugs of pigment or by the parasites may explain the spasms, the convulsions and other neurologic symptoms. In this connection, it is worth while to mention that Meth<sup>43</sup> observed a tremendous number of epileptic patients in the malarial districts of Ecuador. Though he could not confirm his impression by a large number of examinations of the blood, he is inclined to believe that the epilepsy in these cases is due to chronic or to subacute malarial infections.

The second type of malarial psychoses consists of paranoid states, or what Anderson<sup>7</sup> called "delusional psychoses." They include conditions which in the official classification adopted by the American Psychiatric Association are termed paranoid conditions and the paranoid type of dementia praecox. However, in cases of this type slight sensorial changes may coexist. Anderson stated that in most such cases the psychosis started with a state of confusion but that as "the confusion abated, a delusional state emerged and dominated the psychic field. The dominant feature was the persistence of delusions, often of persecutory type." Ferraro and associates,<sup>44</sup> in a study of the cerebral changes occurring with pernicious anemia, reported that minor diffuse cerebral changes may precipitate paranoid reactions.

43 Meth, H. Personal communication to the author.

44 Ferraro, A., Arieti, S., and English, W. H. Cerebral Changes in the Course of Pernicious Anemia and Their Relationship to Psychic Symptoms. *J. Neuropath. & Exper. Neurol.* 4: 217-239 (July) 1945.

The cerebral changes presumably do not cause these paranoid syndromes but probably precipitate them or sensitize the patient to them. This occurs not only with pernicious anemia but with other organic conditions, such as early arteriosclerosis. The changes described in cases of pernicious anemia have a vague resemblance to those accompanying cerebral malaria. Associated with both conditions are alterations of nerve cells leading to the ischemic type, numerous small areas of demyelination, proliferations of the capillary endothelium and occasional ringlike hemorrhages.

The importance of malaria in psychoses of the third type is presumably that of a precipitating factor acting on persons whose capacity of resistance is greatly diminished. The prepsychotic personality may determine the schizophrenic or the cyclothymic manifestations of the psychosis.

The fourth class of psychoses consists of organic mental syndromes, often accompanied with focal signs, such as aphasia and motor disorders. As Huddleson<sup>45</sup> reported, these conditions have no specific characteristics and are indistinguishable from the "psychoses due to disturbance of circulation" such as cerebral embolism, and arteriosclerosis. The pathologic lesions described in cases of pernicious malaria (embolism, hemorrhages, necrotic foci) may well explain the conditions included under this heading.

In addition to these four major types of psychiatric conditions many authors have reported the occurrence of psychopathic or criminal behavior in patients suffering from malaria even after apparent recovery. Some patients presented psychopathic behavior accompanied with psychotic symptoms. Alcoholism (Marandon de Montyel<sup>46</sup>), homicide (Anderson,<sup>7</sup> Dowden<sup>47</sup>, Arcangelo<sup>48</sup>), incendiarism (Betz<sup>49</sup>) and violence and destructiveness (Cardamatis<sup>50</sup>) have been reported as occurring suddenly not only during the febrile attacks but also as a sequel to malaria. These conditions remind one of "the explosive diathesis" described after head trauma. As a matter of fact, the whole classification of malarial psychoses proposed in this report is somehow similar to the classification of post-traumatic psychoses proposed by Adolf

45 Huddleson, J. H. Note on Psychoses and Psychoneuroses with Malaria, *M. Bull. Vet. Admin.* **21** 1-4 (July) 1944.

46 Marandon de Montyel, E. Contribution a l'etude clinique des rapports de l'impaludisme et de l'alcoolisme, *Ann. med.-psychol.* **18** 353-394, 1893.

47 Dowden, cited by Anderson.<sup>7</sup>

48 Arcangelo, S. Un caso di morte violenta in individuo malarico. Con alcune riflessioni sulla malaria, *Comiso*, October 1899.

49 Betz, W. Malaria als oorzak van krankzinnigheid, *Geneesk. tijdschr. v. Nederl.-Indie* **31** 430, 1911.

50 Cardamatis, J. Study of Paludisme, Athens, Levin, 1909.

Meyer<sup>51</sup> This author included with traumatic psychoses a group of post-traumatic deliriums, a second group consisting of psychoses due to a traumatic defect and another group of psychoses in which trauma is merely a contributing factor. One of the most important differences is that paranoid and paranoiac developments seem to be much more frequent with malaria.

The correlation between the psychic sequels and the pathologic process of cerebral malaria has been given special consideration in the present study, in view of its renewed interest in World War II. The evidence would lead one to conclude that whenever a veteran returning from a malarial district shows psychotic or psychopathic manifestations the possibility of malaria as the etiologic factor should be investigated.

#### SUMMARY

Three cases of cerebral malaria due to infection with *P. falciparum* were studied. In case 1, in which the most pronounced changes were presented, the infection was so intense that the malarial pigment contained in the blood vessels made the whole angioarchitecture visible in thick, unstained sections. In this case also, numerous small hemorrhages were particularly frequent in the subcortical white matter and in the molecular layer of the cerebellar cortex. The hemorrhages occurred where the circulation was slowed down on account of the large quantity of pigment or where emboli, consisting chiefly of pigment and parasites, endothelial cells and clotted red cells, had completely occluded the vessels.

The red blood cells appeared to extravasate by a process of diapedesis from a vessel located at the center of the hemorrhagic area. They soon disappeared from the center of the hemorrhagic area, giving the false impression that they came from neighboring, collateral capillaries. Subsequently, the red cells disappeared completely, and demyelination occurred in the same area. At the same time, peripheral proliferation of glia took place. Thus nodules were formed, which did not present inflammatory characteristics and should not be called granulomas, as at times they erroneously have been. In case 1 axonal degeneration of ganglion cells was also shown. Other changes, common to all the cases, were proliferation and desquamation of vascular endothelium, acute swelling of and ischemic changes in nerve cells and hypertrophy and hyperplasia of the glia cells.

Though the state of hyperthermia and the toxicosis were considered responsible for some of the changes, the severest pathologic changes were attributed to the mechanical action of the pigment and of the emboli.

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<sup>51</sup> Meyer, A. The Anatomical Facts and Clinical Varieties of Traumatic Insanity, *Am J Insan* 60 373-441, 1903-1904.

A review of the literature revealed that psychotic conditions occurring during or after malaria may be divided in four types (1) acute deliriums (2) paranoid syndromes, (3) typical psychoses and (4) organic defect syndromes. Psychopathic behavior, with or without psychosis is also common.

The histologic changes associated with cerebral malaria are considered at times the direct cause of and at other times only precipitating factors in the mental syndromes.

It is suggested that when a veteran returning from a malarial district shows psychotic or psychopathic symptoms the possibility of a malarial origin should always be investigated.

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# Abstracts from Current Literature

EDITED BY DR BERNARD J ALPERS

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## Anatomy and Embryology

THE EFFECT OF REDUCTION IN NUMBERS OF OMMATIDIA UPON THE BRAIN OF  
DROSOPHILA MELANOGASTER MAXWELL E POWLER, J Exper Zool **94** 33  
(Oct) 1943

Three stocks of *Drosophila* were established wild type, different combinations of Bar alleles and eyeless-2, which possessed numbers of facets in seven decreasing steps (full eye to total absence of ommatidia) The brains were studied with silver and gold impregnation methods

The chief characteristic related to reduction in numbers of ommatidia is hypoplasia of the optic glomeruli with the elimination of certain histologic traits of the wild type The neurologic effects are localized within the optic lobes

The differentiation and volume of the optic glomeruli are directly correlated with eye size

Total absence of ommatidia is associated with a reduction of 100 per cent of the external glomerulus, 85.4 per cent of the middle glomerulus, 58.7 per cent of the anterior inner glomerulus and 57.1 per cent of the posterior inner glomerulus

The extent of glomerular hypoplasia depends on the percentage composition of the ingrowing fibers which have been eliminated

The volume of the glomeruli is correlated only with the facet number of the adjacent side The ommatidia-glomerulus relationship is autonomous on each side

When no fibrillar attachment is established between ommatidia and the brain the optic glomeruli are histologically and volumetrically like those of completely eyeless flies

The data indicate that the hypoplasia of the glomeruli is not a primary action of the genetic factors but is a secondary result of the ingrowth of a smaller number of centripetal fibers from the genetically reduced peripheral field

REID, Boston

AN IRON-ALUM-HEMATOXYLIN STAINING METHOD FOR MYELINATED FIBERS  
W T NIEMER, J Neuropath & Exper Neurol **3** 419 (Oct) 1944

Niemer describes an iron alum-hematoxylin method for staining myelinated fibers This method can be used on very old formaldehyde-fixed material and even on old material originally fixed in anticipation of using the Weigert method A list of reagents (ferric alum, hematoxylin, ammonium hydroxide, sodium borate [borax] and potassium ferricyanide) and the procedure are described

In sections from non-bichromate-fixed material the gray matter stains light tan to yellow and the white fiber pathways deep blue to black In sections from bichromate-fixed material the gray matter stains light gray to tan and the white matter deep blue In both kinds of material color values make the method particularly desirable for photography

Microscopically, neuron cell bodies are stained yellow, with black nuclei, and red blood cells are stained black The stain differentiates fine and coarse myelin sheaths and fiber bundles cut in slightly different planes

GUTTMAN, Philadelphia

# THE MARCHI REACTION: ITS USE ON FROZEN SECTIONS AND ITS TIME LIMIT

P. GILES, *Brain* **66** 229, 1943

Giles describes a modification of Swank and Davenport's method of Marchi staining. Tissues are fixed in solution of formaldehyde U S P (1:4) up to forty-eight hours, washed in 1 per cent potassium chloride for ten minutes and then stained in Marchi solution for about ten days. Frozen sections are then cut and may be counterstained with toluidine blue or light green. According to Giles, preparations treated as he describes show clearly the degenerated fiber tracts and pseudo-Marchi granules are rare.

Giles points out the lack of uniformity of opinion regarding the optimum time for study with the Marchi method after the production of a lesion. In rabbits and cats he believes the optimum time to be at least three weeks. With regard to the length of time in which positive staining can be obtained after the production of a lesion, Giles found time intervals as great as one year for cats and rabbits. The author points out the need for care in interpreting the Marchi reaction in animals subjected to two ablations.

FORSTER, Philadelphia

## Physiology and Biochemistry

### ON THE QUANTITATIVE INCIDENCE OF CARBONIC ANHYDRASE IN THE CENTRAL NERVOUS SYSTEM

W. ASHBY, *J Biol Chem* **155** 671, 1944

In a previous paper data were presented indicating that in seven species of animals studied, including man, the carbonic anhydrase content of the spinal cord was approximately half that of the cerebrum. The data further indicated that this was not due to any differences in the relative amounts of the gray and the white matter in the samples chosen or to the enzyme accounted for by blood content. The hypothesis was advanced that the greater enzyme content was associated with quantitative metabolic differences between the two areas which would play a part in establishing their respective functional levels. It was suggested that the enzyme was either in the neurons or in cells accessory to them and that it was either produced *in situ* or absorbed from the blood corpuscles, which contain it in large amounts. In the latter event, differences in content perhaps due to differences in circulatory activity would represent a result of function but might, in turn, modify metabolism differentially. Carbonic anhydrase is found in the central nervous system of various species of animals in patterns which tend to be peculiar to the species. Carbonic anhydrase content has been found to increase progressively rostrally. The enzyme is found in the white matter in some instances in greater amount in the white matter than in the gray. It is possible that it functions more specifically with reference to the nerve fiber.

PAGE, Cleveland

### THE EFFECT OF INGESTED CHOLINE ON THE TURNOVER OF PLASMA PHOSPHOLIPIDS

H. D. GRIFFIANDER, I. L. CHAIKOFI and C. ENTINMAN, *J Biol Chem* **158** 231, 1945

With the use of labeled phosphorus ( $P^{32}$ ) it was shown that ingested choline speeds up the rate of phospholipid turnover in the liver. Betaine had a similar action, but its effect was less pronounced than that of choline. As a result of these, and other, observations it was pointed out in 1939 that phospholipid synthesis by the liver is an important intermediary step in the removal and deposition of fat in the liver. The effect of choline on the renewal of phospholipid phosphorus in the plasma was studied in dogs fed a high fat, low protein diet. Radioactive phosphorus was used as the labeling agent. A single feeding of 300 mg of choline chloride per kilogram of body weight accelerated phospholipid turnover in plasma. Choline increased the rate of change in the specific gravity of phospholipid phosphorus of plasma during the early intervals after the administration of radioactive phosphorus. The maximum values found for the specific activity of phospholipid phosphorus of plasma were higher in dogs fed choline than in those not fed choline.

PAGE, Cleveland

INTRACENTRAL AND PLRIPHIRAL FACTORS IN THE DIFFERENTIATION OF MOTOR NIURONS IN TRANSPLANTID LUMBO-SACRAL SPINAL CORDS OF CHICK EMBRYOS ELMIR D BUEKLR, J Exper Zool **93** 99 (June) 1943

Unilateral extirpations of limb primordia and transplantations of the lumbo-sacral segments of the spinal cord of 52 to 68 hour chick embryos were made in order to analyze the role of peripheral fields and of longitudinal fiber tracts in the quantitative differentiation of motor neurons in the spinal cord

After limb extirpations hypoplasia of motor neurons representing a reduction of 75 to 90 per cent occurs This reduction is even greater in limbless transplants

A lumbosacral plexus is not formed on the limbless side in transplantation or extirpation experiments

In several transplants with one well developed limb attached the number of motor neurons was normal on the limb-innervating side

The results, a growth reduction of 50 per cent in spinal ganglia in the absence of limbs, correspond with the observations of Detwiler and of Hamburger

The shortening of segments of the spinal cord during development is associated with fusion of ganglia or their approximation Segments are frequently resorbed from the ends of transplants, and the remaining segments are often incomplete The motor neurons are affected most seriously, and the median parts are involved less seriously than the sensory column

Dorsal sensory areas of the gray matter and dorsal and ventral roots are reduced by the removal of limbs

The author concludes that the development of the lateral motor column of the spinal cord depends on the presence of a developing limb and the pelvic girdle However, connections with descending fiber tracts are not essential for the development of the lateral motor column of the spinal cord

REID, Boston

EXPERIMENTAL HEAD INJURY WITH SPECIAL REFERENCE TO THE MECHANICAL FACTORS IN ACUTE TRAUMA E S GURDJIAN and J E WEBSTER, Surg, Gynec & Obst **76** 623 (May) 1943

In the experience of Gurdjian and Webster, the physiologic effects of head injury seemed generally to have been correlated with the intensity of the injury and the pathologic changes produced in the brain To verify this impression, experiments were undertaken with the dog as the test animal Morphine anesthesia was used, and the striking force was applied directly to the parieto-occipital bone, the scalp and the masseter muscle having been reflected from the bone The state of consciousness was determined by the animal's response to pressure applied to the tail and paws

The experiments were divided into three groups (1) 30 experiments in which dogs were injured by a falling weight or a hammer blow striking the fixed head, (2) 70 experiments in which the nonfixed head was struck, the hammer, a pendulum and a spring device being used as the injuring force, in about an equal number of experiments, and (3) 38 experiments with injuries of a penetrating type, including gunshot wounds

Three levels of physiologic response were seen 1 Minimal tolerance to the injury, with no significant changes in the blood pressure, respiration or reflexes all the animals survived 2 Moderate cessation of respirations or interruption in corneal and palpebral reflexes All these animals lost consciousness, but most of them were able to survive the injury 3 Profound death of the animal during the acute experiment A remarkable, temporary rise in blood pressure with tachycardia was characteristic

The skull was practically always fractured, this being necessary for even a moderate effect It was not possible to produce profound physiologic effects without pathologic damage to the brain, and only in a few instances was unconsciousness produced without associated gross pathologic damage to the brain Physiologic responses were preportional to the degree of pathologic damage



Fatalities occurred only if severe cerebral damage had been produced. Consciousness was generally depressed in animals showing minimal response, lost for prolonged periods in animals showing a moderate response and lost until death in animals showing a profound response. Loss of the palpebral and corneal reflexes represented a more profound response to injury than did unconsciousness. A remarkable rise in blood pressure was usually observed after injury in animals showing moderate and profound responses being prompt and as high as 300 mm of mercury. The maximum rise was maintained for sixty to one hundred and sixty seconds in the group with moderate responses and for one hundred and eighty seconds in the group with profound responses and gradually fell to zero at the death of the animal. Tachycardia always accompanied this phenomenon. The rise in blood pressure failed to occur if the skull and brain were particularly crushed by the injury or if the spinal cord was transected at the first thoracic level. Removal of both adrenal glands failed to prevent the rise in blood pressure, but yohimbized animals which did not respond to epinephrine showed no increase in the blood pressure after profound injury. The blood flow was decreased in the spleen and increased in the hindpaw, a response which further emphasized the role of the sympathetic nervous system in this post-traumatic type of hypertension.

There was no significant rise in spinal fluid pressure after closed injury to the head. The amount of blood in the spinal fluid was usually commensurate with the intensity of the head injury. Supratentorial gunshot wounds were noted to give intensely increased intracranial pressure at the instant of injury. This was indicated by extension of the cerebellum through a suboccipital craniectomy opening. A gunshot injury 5 cm below the medulla with transection of the cord, resulted in contusions of the cerebral cortex.

Penetrating gunshot injuries of the brain resulted in acute physiologic effects, similar to those which were noted with the other forms of trauma.

In these experiments a velocity range of from 13 to 40 feet (4 to 12 meters) per second was developed. When the head was allowed to move, higher velocities were required to cause a given injury than when the head was fixed. The acute effects of a blow to the head are proportional to the rate of change of the momentum of the striking force. The effects of a cranial trauma are due to a number of factors, which include (1) a sudden increase in the intracranial pressure at the instant of injury, (2) mass movements of the brain and (3) a diffuse cellular disturbance, due to transmitted energy with no accompanying increase in intracranial pressure.

SHANKIN, Philadelphia

#### STUDIES IN DENERVATION J. DOUPE and Associates J. Neurol & Psychiat 6 94 (July-Oct) 1943

*Methods*—Doupe and his co-workers carried out a number of investigations on patients with lesions of the peripheral nerves. The methods used consisted in measuring the peripheral circulation by means of recording cutaneous temperatures of the finger pads, supplemented in some instances by plethysmographic records of the digits. Various measures to modify the circulation, such as local effects of moderate to extreme cold or heat and injections of epinephrine, were used.

*The Circulation in Denervated Digits*—Investigations were carried out to test the validity of the hypothesis of Lewis and Pickering that sympathectomized limbs stay warm while denervated digits become cold. Observations were made on subjects with preganglionic and ganglionic sympathectomies and on subjects with lesions of peripheral nerves. Doupe concluded that, contrary to the results of Lewis and Pickering, the digital vascular reactions are similar in the two groups of patients. The cause of the usually diminished circulation in denervated digits is sensitization to cold produced by degeneration of the sympathetic fibers. This sensitization is made the more manifest by the action of circulating epinephrine,

by the action of vasomotor fibers still supplying the limb and by variations in local and general blood pressure. Part of the difference in the state of denervated and ganglionectomized digits may be ascribed to the persistence in the latter of some postganglionic fibers. The reactive hyperemia which has been observed in denervated digits is in part mediated by arteriovenous anastomoses, is not dependent on any neural mechanism, is greatly slowed by a high sympathetic vasoconstrictor tone and is not affected by the vasoconstriction caused by cooling the denervated digit. Denervated blood vessels appear to be histologically normal. There is no correlation between Raynaud's syndrome and sensitivity associated with denervation. In the former condition there is no hypersensitivity to epinephrine. In the latter there is no history suggestive of vasospasms, the cyanosis is slight and there is a ready response to reactive hyperemia. Thus, with lesions of peripheral nerves the blood flow is adequate to the needs of the tissue, while with Raynaud's syndrome ischemia occurs. The trophic changes in denervated digits are attributed to the lowered tissue metabolism consequent on the persistent coldness, since the blood supply is adequate. The sensitivity to cold in denervated digits may be explained on the basis of changes in hydrogen ion concentration, since a fall of temperature would directly raise the  $p_H$  and produce vasoconstriction, or decrease the formation of acid metabolites and thus indirectly lead to elevation of the  $p_H$  and vasoconstriction. The regain of tone following denervation is ascribed to the action of local influences on sensitized vessels. A circulating vasoconstrictor substance in the blood may only be assumed in the case of systemic disorders.

*Inflammation and Trophic Ulcers in Denervated Areas*—Slow healing of trophic ulcers, produced by burns or pressure, in denervated digits has been ascribed to diminished blood supply. Since the authors contend, however, that the blood supply of denervated digits is adequate, there must be other causes for the delayed healing. In the case of ulcers following burn, the slow healing is only apparent, since data are lacking on the extent of the original trauma because of loss of pain sensation in the denervated area. In the case of ulcers produced by pressure slow healing is due to edema associated with impairment of the lymph drainage in the extremity. The occasional presence of a vesicular eruption in cases of peripheral nerve lesions also is due not to denervation but to a variety of cheiropompholyx.

*Mechanism of Axonal Vasodilation*—On the basis of a case of section of the ulnar nerve, Doupe concludes that axonal vasodilation is mediated by fibers other than those associated with sensation. The mechanism of axonal vasodilation is still obscure. According to Lewis, it depends on efferent cholinergic fibers having their trophic center in the posterior root ganglia and distributed in the skin in the form of a plexus, stimulation of which releases the so-called H substance. A review of the literature fails to corroborate this view. The authors offer an alternate hypothesis, viz., that the fibers subserving axonal vasodilation are afferent and that they terminate in a branching axon system with receptors specially sensitive to products of tissue damage, similar to histamine. Axonal vasodilation is thus attributed to the metabolites of nerve fibers, rather than of cells of the skin.

*Epinephrine*—Denervation of digital vessels in human subjects renders them hypersensitive to the vasoconstricting action of epinephrine. This is due to degeneration of sympathetic fibers, which produces in the vessels of denervated digits a lowered threshold and a prolonged response to the action of epinephrine. The vessels of preganglionectomized digits, on the other hand, show only a lowered threshold. This difference between degenerative and nondegenerative section of sympathetic nerves is due to a loss of "accommodation" in the former which is not present in the latter. Emotional stimuli cause a release of epinephrine in the body, but the need for heat conservation is a more variable and less constant cause of such liberation. Thus, the original view of Cannon that secretion of epinephrine is associated with mental excitement is more correct than his later

assumption that epinephrine participates in many of the ceaseless variations in body function. Peripheral neurogenic vasoconstriction is not necessarily accompanied with the release of epinephrine, an indication that within the sympathetico-adrenal system different patterns of behavior are elicited by stimuli of different types. Epinephrine could be liberated in the body in amounts comparable to the rapid intravenous injection of 2 micrograms or to injection of the drug for longer periods at the rate of 6 micrograms per minute. In other circumstances, much larger amounts might be liberated, which would suffice to initiate persistent vasoconstriction in a denervated digit.

*Circulation in the Skin of the Proximal Parts of the Limbs*—Doupe and his collaborators confirmed the view expressed by Grant and Holling that there exists a vasodilator sympathetic supply to the blood vessels in the skin of the proximal parts of the limbs by producing active vasodilation in response to intense heating of the body. The lack of effect of nerve block when the subjects are cold shows that there is no significant vasoconstrictor innervation of the vessels in these areas of the skin. The vasodilation is not dependent on the activity of the sweat glands, since the action of the latter can be abolished by atropine without thereby decreasing the vasodilation. The thesis of Grant and Holling is not refuted by the occurrence of vasodilation following sympathectomy. The latter phenomenon may be due to discharges in vasodilator fibers, which are decentralized by the operation, to the anesthetic and to absorption from traumatized tissues.

*Sebaceous Secretion*—The author and his co-workers estimated the sebaceous secretion in a subject with a sympathectomy and in another subject with a lesion of the brachial plexus. They found that the sebaceous glands can function in the absence of all nerve fibers. Similarly, the growth of hairs and the metaplasia of the cells of the epidermis are unaffected by deprivation of direct nerve influences. Sebaceous secretion is thus simply a manifestation of the growth of the cells of the sebaceous glands. The physical state of the skin influences the production and absorption of the sebaceous material. The abundant secretion in cases of lethargic encephalitis may be due to disturbances in hormonal regulation.

*Effect of Electrical Stimulation on the Circulation and Recovery of Denervated Muscle*—The value of electrical treatment of denervated muscles was investigated in a series of 12 patients after suture of the musculospiral or the posterior interosseous nerves. It was found that electrical treatment had no beneficial effects on the return of motor power. This failure was ascribed to the fact that the treatment does not impose a strain on the muscles of sufficient intensity to be of therapeutic value. The amount of electrically induced exercise was estimated by using the rate of blood flow as an index, and it was found that even more intensive stimulation produced a relatively slight increase in blood flow. The only benefit derived from electrical therapy is in induction and reeducation of muscular movements.

*Contractility and Excitability of Denervated Muscles*—The electrical reactions of denervated muscles consist in changes in contractility and excitability. Repetitive excitation is likely to develop in denervated muscle when it is subjected to an electric current. This phenomenon is a persistence of potentials throughout the phase of muscle shortening, due to the fact that each muscle fiber is responding more than once. It is readily produced by a constant current. The phenomenon of galvanotonus is also attributed to the repetitive firing of the muscle fibers. Denervated muscles usually show prolonged contraction, which is due to repetitive stimulation by constant currents in conjunction with a cool state of the muscle. Similarly, denervated muscles show prolonged excitation, which is also due to repetitive stimulation plus the relation of the muscle fibers to the field of the current. Electrical reactions are of clinical value only when positive, for when negative they may be attributed to factors other than the state of degeneration of the muscles.

MALAMUD, San Francisco

## Neuropathology

THE EFFECTS OF IODIZED POPPYSEED OIL AND IODINE-CHLORINE IN PEANUT OIL IN THE SUBARACHNOID SPACE OF ANIMALS EDWIN BOLDREY and ROBERT B AIRD, *J Nerv & Ment Dis* 99 521 (May) 1944

After the fall of France, in 1941, the authors undertook to find a satisfactory substitute for 40 per cent iodized poppyseed oil, which was no longer available. For this purpose, 27 per cent iodine and 75 per cent chlorine in peanut oil (Iodo-chlorol) was selected and was tested for comparison with 40 per cent iodized poppyseed oil. In a group of dogs, 2 cc of the radiopaque substance was injected into the subarachnoid space through the cisterna magna. Four dogs received an additional injection after a week's interval, and another group of 4 dogs received 2 cc of oil plus 2 cc of the animal's own freshly drawn blood. On 2 animals which had received the Iodo-chlorol and on 1 which had been given an injection of iodized poppyseed oil autopsies were performed on the fourth or fifth day. Mild subarachnoidal and adventitial inflammatory changes were noted in the cervical region in all the dogs. Two dogs, followed for eighty-six days after the injection of iodine and chlorine in peanut oil, showed a transient rise in the spinal fluid of polymorphonuclear leukocytes and lymphocytes, and autopsy showed definite gross adhesions in the upper cervical region and numerous thick-walled cysts about the brain stem. In a similar experiment, in which 2 dogs received iodized poppyseed oil, the transient rise in the cell count was higher in each instance, and the pathologic changes were more extensive and severe. Animals which had received two injections of either iodized poppyseed oil or the iodine-chlorine preparation showed a more pronounced reaction than those which had had only one injection, this was especially true if a relatively long time was allowed to elapse after the second injection before the dog was killed. In other animals, the addition of blood to the injected oil materially increased the irritating effect.

The most significant observation was the progressive chronic adhesive reaction found after three months in animals given injections of either of the oils. Although the reaction with the iodine-chlorine preparation was slightly less than that with the iodized poppyseed oil, there was sufficient reaction in either case to make the removal of the oils from the subarachnoid space desirable.

CHODOFF, Langley Field, Va

VASCULAR CHANGES IN EXPERIMENTAL ANAPHYLAXIS OF THE BRAIN A FERRARO, *J Neuropath & Exper Neurol* 4 1 (Jan) 1945

Ferraro reports observations on the brains of monkeys which were subjected, over varying lengths of time, to parenteral injections of egg white. Histologic study revealed that if an animal died soon (fifteen hours) after an intracerebral injection typical features of the Arthus phenomenon, with necrosis, hemorrhages, edema and perivascular reaction, consisting mainly of the presence of polymorphonuclear leukocytes, were seen. In an animal which survived six days after the last intracerebral injection of antigen the perivascular reaction showed a mixture of polymorphonuclear leukocytes and lymphocytes. In other monkeys in which the injection of antigen was prolonged for a much greater period the perivascular reaction was characterized by the presence of lymphocytes associated with large mononuclear cells. The longer the period of sensitization, the more dominant was the lymphocytic-histiocytic type of reaction. In addition, the formation of giant cells, derived either from large mononuclear cells or from histiocytes, became an added important histologic feature. The presence of the typical Arthus phenomenon was therefore not essential in determining the anaphylactic origin of a pathologic process.

In another series of experiments in which the antigen was administered intramuscularly, some of the animals were given injections for a long period without presenting clinical symptoms of involvement of the central nervous system whereas

under identical conditions other animals died after a number of injections, which varied from 29 to 103. The sensitization of the animal took a minimum of one hundred and twelve days and a maximum of four hundred and five days, and the histologic changes were similar to those seen in the later stages of experimental anaphylaxis, namely, the lymphocytic-histiocytic type accompanied with varying degrees of parenchymatous change, ranging from minimal alteration to necrosis. The necrosis was independent of the hemorrhages with which it was associated in the acute stage of the reaction.

GUTTMAN, Philadelphia

A CASE OF PERIARTHRITIS NODOSA WITH DISCREPANT RIGIDITY AND EXTENSIVE ENCEPHALOMALACIA IN A FIVE YEAR OLD CHILD. N. MALAMUD, *J Neuro-path & Exper Neurol* 4:88 (Jan) 1945

Malamud reports the case of a 5 year old boy who, while convalescing from an infection of the upper respiratory tract, had fleeting pains in the joints and abdomen. Examination revealed a systolic cardiac murmur, elevated temperature and leukocytosis but no swelling or redness of the joints. Acute rheumatic fever was suspected. One week later the symptoms began to subside, but the patient suddenly had a series of seizures, became comatose and exhibited decerebrate rigidity. Tendon reflexes could not be elicited, and there were no signs of involvement of the pyramidal tract. The pupils were dilated and fixed to light, and there was mild papilledema. Lumbar puncture and studies of the cerebrospinal fluid revealed nothing significant. Ventriculographic studies suggested the presence of a tumor of the brain stem. The patient died about two and a half months after the onset of his illness.

There was massive necrosis of the cerebrum, while the brain stem and cerebellum were of normal consistency and the basal vessels were soft and delicate. Microscopic observation revealed complete destruction of the cytoarchitecture, with few or no nerve cells remaining, and the brain tissue was replaced with vacuoles of varying sizes or with amorphous masses of precipitate. Within the necrotic tissue a very active mixed mesenchymal and glial reaction occurred. There were marked proliferation of neuroglia and an equally intense proliferation of reticulum fibers, with newly formed blood vessels. The neuroglial reaction was moderate. In the leptomeninges there were a few polyblasts and lymphocytes. The white matter showed intense, but more patchy, involvement. Extensive necrotic changes were also found throughout the optic chiasm, the caudate nucleus, the putamen and the globus pallidus. The thalamus, with the exception of the centromedian and intralaminar nuclei, was destroyed, partly as the result of secondary degeneration. The hypothalamus and the subthalamus were only slightly involved. The necrosis terminated at the level of the red nucleus. The brain stem and the spinal cord exhibited only mild secondary degeneration of the pyramidal tracts. The cerebellum, however, showed pronounced diffuse degeneration of nerve cells in the Purkinje layer and the dentate nucleus. Study of the meningeal and cerebral blood vessels revealed lesions in a subacute phase of hyaline necrosis of the subintima and media, perivascular infiltration with lymphocytes and fibroblastic proliferation of adventitia and intima, encroaching on the lumen. Similar vascular lesions were found in the heart, and somewhat more chronic ones were noted in the walls of the trachea, the esophagus and the gastrointestinal tract and in the kidneys.

Anatomically, there was a conspicuous discrepancy between the extensive destruction of the cerebral parenchyma and the restricted vascular lesions. The discrepancy between the involvement of the parenchyma and that of the vascular system may be of significance in understanding the nature of the disease. Malamud states that the onset following an infection of the upper respiratory tract and its initial general effect on various organs, followed by an intense necrotizing process in the brain, clearly out of proportion to the extent of the arteritis, suggests an allergic reaction.

GUTTMAN, Philadelphia

## Psychiatry and Psychopathology

PSYCHOSES OCCURRING IN SOLDIERS DURING THE TRAINING PERIOD MARGARET HITSCHMAN and ZULEIKA YARRELL, *Am J Psychiat* **100** 301 (Nov) 1943

Hitschman and Yarrell studied 100 soldiers who were admitted to the psychiatric division of Bellevue Hospital. One third had enlisted, the remainder were drafted. Only 1 had seen actual combat. The distribution of diagnoses was as follows: schizophrenia, 78; manic-depressive psychosis, 8; psychopathic personality, 6; psychoneurosis, 4; mental deficiency, 1; epilepsy, 2; and syphilis of the central nervous system, 2. Thirty-one of the 100 men had had previous psychiatric treatment. In correlating the length of service with the onset of the illness, the authors found that 70 of the group became ill within five months of entering service. On reviewing the preinduction histories, the authors found that 38 had made good adjustments. Twenty-three of the 100 men became ill within the first two weeks of service, and in this group the authors felt that military service played a role as a precipitating factor. In a comparison of the clinical features of the psychoses found in these soldiers with those in a group of civilians of similar age and sex, no significant difference was apparent. In order to lower the incidence of psychiatric casualties, the authors recommend social investigations to eliminate men with previous admissions to mental disease hospitals, investigation of police and social agency records, a three months' probationary preinduction period, special training units in replacement centers and psychiatric examination of maladjusted soldiers after three months.

FORSTER, Philadelphia

CLINICAL AND EEG STUDIES IN OBSESSIVE-COMPULSIVE STATES B. L. PACELLA, P. POLATIN and S. H. NAGLER, *Am J Psychiat* **100** 830 (May) 1944

Pacella, Polatin and Nagler studied the electroencephalograms of 31 patients with obsessive-compulsive states. Twenty-six of these patients were classified as psychoneurotic, and 2 of them had petit mal attacks in addition to their obsessive-compulsive state. Five patients had schizophrenia. Twenty of the 31 patients had abnormal electroencephalograms, 14 of whom presented occasional or frequent runs of 2 to 4 per second, high voltage activity. In most records the paroxysmal disturbance was apparent only after hyperventilation. Only 9 of the 31 patients had definitely normal records. The patients under 30 years of age had a greater incidence of abnormalities in the electroencephalogram. There was some indication of a higher incidence of a family history of psychopathy in the group with abnormal electroencephalograms, but the authors conclude that the differences, while suggestive, are not statistically significant. The severity of the clinical symptoms could not be correlated with the electroencephalographic pattern.

FORSTER, Philadelphia.

A RUNAWAY FROM HOME HUGO STAUB, *Psychoanalyt Quart* **12** 1, 1943

Although many elements participate in the production of a criminal, among which are economic and social factors, traditions, the level and form of civilization, politics, power and psychologic factors, Staub doubts whether there is a genuine criminal who is not one because of an inner conflict, i. e., anxiety feelings, feelings of guilt or a need for punishment. Reality often replaces the inner mechanisms of guilt and self punishment by pressing hard enough and by inflicting sufficient suffering to weaken the inner restrictions and relieve the inner anxiety, thus releasing the aggressive tensions. The author believes that in all criminals there is an emotional urge to act dissocially, which originates in an unconscious conflict. In prison a criminal may be calm and well adjusted, but when he is released he becomes shaky, disintegrated, unbalanced, inhibited and emotional except when committing a crime. The interplay between the reactions of society and the criminal's acting out of his unconscious fantasies of self punishment result in the

development of a criminal character in the latter. In proof of his thesis, Staub offers the analysis of a 17 year old boy who showed a compulsive tendency to run away.

The author emphasizes two points in discussing the case.

1 Running away is behavior which is in contradiction to the tendency of a child to cling to infantile dependencies. The child may run away because he is being treated badly in his home, or he may run away, as in the case cited, because he has feelings of guilt about his unconscious murderous and incestuous impulses. With the latter motive there are associated some pleasure gains—by running away the child can make his mother cry for him and want him back, he can take revenge on her, and he can imitate his father by appearing capable and self reliant.

2 In treating patients whose behavior is antisocial, it is necessary to modify the usual psychoanalytic procedure. Such patients are at first absolutely passive in treatment because they have strong feelings of frustration and disappointment to which they react by obstinacy. The analyst must be active in convincing the patient of his willingness and ability to help and of his perception of the patient's inner problems. The patient will test the analyst by every means possible to see whether he means what he says. If the patient is a braggart, he must be shown that his exaggerated self confidence is an overreaction to his feeling of helplessness. He must be helped to lose his anxiety about his helplessness by his confidence that the analyst will stand behind him. With the adolescent, the analyst must appeal to his intelligence. The analyst's activity in this preparatory period is directed toward gaining the patient's confidence in order to establish a strong positive transference, to draw off the excess of anxiety and fortify the badly damaged self confidence and to permit the controlling and restraining forces of the ego to operate. This accomplished, the usual technique of psychoanalysis is employed.

PEARSON, Philadelphia

# Society Transactions

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## PHILADELPHIA PSYCHIATRIC SOCIETY

O Spurgeon English, M D, *Presiding*

*Regular Meeting, March 9, 1945*

### Modern Concepts of the Convulsive State DR TEMPLE FAY

The use of insulin, metrazol and electric shock has made the convulsive seizure such a commonplace event that the psychiatrist and the public as well have abandoned the concept that such attacks are evidence of mental inferiority and degeneration. With this remarkable change in concept there is a recurrence of many challenging questions.

The concept that the convulsive seizure may be a latent pattern of an early evolutionary type of reaction pattern, at approximately the level of the amphibian, seems worthy of consideration in view of the fact that the pattern of movement never includes the acquired skilled activity and the coordinated types of action patterns seen in the forms above the mammalian level.

Many circumstances surrounding a seizure cannot be harmonized with the concept of an "irritative" or a "stimulative or overflow" response. The latent period existing between the application of a stimulus to the brain organ and its response in terms of a typical convulsive seizure has not received the attention or consideration it should. Stimuli applied to peripheral nerve roots or to the cord itself yield an immediate and violent response.

Instead of electric shock stimulation being the cause of the motor discharge, the latent interval may well be concerned with the effects of stunning or removing the inhibitory influence of the cortex so as to permit spontaneous release of lower levels of motor activity similar to the early phylogenetic pattern.

The former concept of a convulsive seizure being "an evil discharge of purposeless movements" has given way to a more rational consideration of the removal of higher evolutionary dominance in terms of motor patterns and cerebral levels, rather than of direct "irritation or discharge of cortical energy" from pathologic areas adjacent to the motor cortex.

### Drawings of a Seven Year Old Child DR ROBERT S BOOKHAMMER

Drawings by a 7 year old girl depicted a boy having his genitals cut off by a large knife in the presence of little girls, who were making fun of the situation. The child was reported to be quite a tomboy, definitely regretting that she was a girl. The drawings were viewed as an attempt to resolve her conflicts in relation to this envy, thus enabling her to become more accepting of her femininity. They were offered as an addition to the ever increasing data supporting the theories related to the little girl's concern with her lack of a penis. It was emphasized that this child was in normal health and occupied with the normal problems of her psychologic development.

#### DISCUSSION

DR GERALD H J PEARSON All of us who do any type of psychotherapy are always glad to have objective evidence from children which bears out some of the inferences we draw of what goes on in the subconscious mind of the adult patient. It is always good to have objective material that will show these conflicts as they develop and the way in which the child learns to handle them.

It is important that these drawings came from a normal child. One sees many drawings like this in psychiatric work with sick children. There is no question that the drawings show that this little girl is having a hard time reconciling



herself to the fact that there are creatures in the world who are not the same as she is

The father picked these drawings out of the wastebasket, where the child had thrown them. At the same time, he noticed that the child seemed to be a little upset in relation to her brother. Perhaps many parents would have spanked this little girl and said that she was naughty. When a parent is able to get material produced by the child showing that the child is having an emotional problem, they could do something to help the child during this period. Emphasis should here be put on the fact that it is "just as important to be a girl as a boy."

DR JOSEPH C YASKIN Did Dr Bookhammer say this child was 7 years of age when these drawing were made? How reasonably certain is he that she really is well?

DR HAROLD D PALMER What criterion does one use in saying "a perfectly normal little girl"? This child had anxiety, a great deal of anxiety. She put the drawings where they would be found. She put them there with the intention of punishment. A child of 7 is clever enough to have disposed of them, and she would not have put them where they would have been discovered by the parents if she had not wanted them to be found.

DR O SPURGEON ENGLISH That there is an inherent tendency toward destruction in human beings, whether male or female, is here shown pretty clearly. Freud spoke of the death instinct, and Menninger developed it further in "Man Against Himself" and showed how many different forms this instinct takes in human beings.

One sees so much envy and jealousy, criticism and destruction in the world. It is very common. A woman will envy another woman her appearance, another her good looks and another her ability and talents in some field and can feel only unhappy about it and want to criticize her. Men envy each other their physical prowess and ability, instead of emulating each other.

Such aggressive and destructive trends show how much help children need in early life, how much attention one needs to pay to satisfying sexual education.

Whatever one's opinion may be about the castration complex as a theory, one will surely agree that children need a great deal of help and direction in how to accept themselves as they are. They need much help and proper direction of such destructive tendencies as are shown in this child, whether she is regarded as sick or normal.

DR ROBERT S BOOKHAMMER I purposely made this communication short and did not go into a considerable history of this child. If I had gone into it more deeply, perhaps some of these questions would have been anticipated and answered.

Dr Yaskin will have to take on faith my statement that she is well. I have known this little girl fairly well over a period of years. She is perhaps in the upper third of her class in school and is very popular with the other children. She presents no behavior problem, either in or out of the home. She is happy and contented. She shows no particular phobias or obsessions or anxieties beyond the usual range of childhood.

In answer to Dr Palmer's question. This child has been perhaps a little more fortunate than most in growing up in a household where there has never been much restriction of any sort on expression. Since she has been able to draw, she has drawn pictures of animals, in which she includes the genitalia of the animals and draws only male animals, never females.

I suppose every 7 year old girl has a certain amount of anxiety, and this child's need to express her problems in these terms indicates that she has anxiety. I do not think that such anxiety in a 7 year old girl is necessarily pathologic. Every little girl has this kind of anxiety, which she has to work out in some way or other, and this seems a pretty good way of doing it.

## Utilization of a Therapy Group in Teaching Psychotherapy DR SAMUEL B HADDEN

Four years ago students and interns interested in psychiatry began attending sessions of the psychotherapy group at the Philadelphia General Hospital, and in the fall of 1944, 15 students, volunteers, were selected to work with men discharged from the services for psychoneurotic disabilities or rejected for service for the same cause

Each student is assigned a new patient, takes the history, carries out the indicated examinations and usually arranges a weekly conference other than the interview at the group discussion. After twenty to forty minutes spent in personal interview between patient and student, both gather with the leader for group discussion. New patients are admitted at any time, giving opportunity for repetition of essential principles, such as repression, sublimation, projection and introjection. The patients understand the sessions are part of the teaching of the students and accept their student-doctors confidently. At times the students are assigned topics which they present to the group and which are the subject of discussion by both patients and students.

The purpose of the course was to give students an appreciation of the psychotherapeutic procedures, and the students have reported that they have acquired an understanding of themselves as well and that their personalities have been favorably affected. They have unanimously stated that this was the first opportunity they had had of working with psychiatric patients on an intimate basis. Many expressed surprise that the symptoms of neurotic patients were accepted as being real and that such symptoms as tachycardia, epigastric pain and digestive disturbances could be influenced by psychotherapy. At first they regarded with skepticism the assurance of improvement in patients without medication. The students felt that at least two, or even three, sessions a week were in order.

### DISCUSSION

DR ROBERT A MATTHEWS For the past twenty years there has been a gradual and, I should say, satisfying improvement in the teaching of psychiatry all over the country, especially in the better medical schools. It can be best presented didactically through student clinics and with student work in the wards.

My associates and I are still trying to find a way to present adequately the problems of the psychoneuroses and the psychosomatic problems. We have tried a lecture form, and I am fairly convinced that we did not succeed very well in presenting didactically material regarding the understanding and treatment of the psychosomatic patient.

We have tried the presentation of psychoneurotic patients before large groups of students. At one time I thought this method was not feasible, but the more I see of it the more I believe that one can present psychoneurotic patients to large groups of students, actually discussing the patient's problem before a student group. However, that still does not solve the problem of allowing the student to get the feel of the psychoneurotic problem.

Dr Hadden has shown one of the ways in which one may be able to do this. Students, in this plan, are allowed to talk to individual patients. Then the group gathers together, and certain basic principles are discussed and the patients are encouraged to discuss their own problems. This permits a combined individual and group interview, which, I think, is excellent. The trouble is that at present there are not enough psychiatrists to guide the students in their individual interviews. I think Dr Hadden has presented something that is really stimulating. Medical schools cannot consciously continue to send students out so poorly prepared in this most important of all subjects.

One must be careful that one does not make psychotherapy seem too easy to the student. A certain type of patient who applies at this sort of clinic may not represent the entire cross section of the psychoneurotic problem, and we may be a little careless, if we do not watch ourselves, in not giving the student a healthy respect for the difficulties in this type of treatment. This facile handling of the problem is illustrated in "Lady in the Dark," in which, after four or five sessions, the conflict seems unearthed and the patient married the man of her choice, gets better and lives happily ever after. The student must not think that he will get to the deeper layers of the personality in such group meetings, as can be done only through individual interviews, in many cases extending over long periods. Dr Hadden is to be congratulated in his untiring efforts.

DR JOSEPH C YASKIN. It is not necessary to comment on the value of Dr Hadden's paper. That is self evident.

It might be of interest to look back and see why such methods were not available years ago. I believe that the answer is to be found in the fact that the teachers of a generation ago did not know much about the psychoneuroses and could not teach them. I believe that they would teach the neuroses very sensibly by reason of their personal insight, but they did not have any semblance of a systematic approach.

If a patient has a cerebral tumor or gallstones, he calls a surgeon, whereas the general practitioner has to handle the psychoneuroses. Therefore, he should be better able to manage them.

DR ISADORE RODIS, Washington, D C. Dr Hadden has established a precedent. The psychiatrist is coming out of his ivory tower and getting in contact with the students.

At Georgetown University the students are appreciative of the fact that they can see the psychiatrist and can talk with him. My colleagues and I have found this valuable in the outpatient department and in conferences held by the department of medicine, in which the department of psychiatry has been invited to participate and in which the sessions have been so arranged by the department of medicine that the patient with a psychosomatic disorder is presented to the section of students by the students themselves.

DR GEORGE D GAMMON. The reaction of various departments of the hospital to this plan of group psychotherapy has been rather interesting. In some departments there were physicians who were enthusiastic about referring patients, for instance, the clinic for gastrointestinal diseases, which abounds in such problems. Certain other departments, where elixir of phenobarbital flows freely, have refused to give up their patients. Dr Hadden decided to undertake the treatment of a group for veterans which would meet at night. In order to get assistance for that, it was decided that the senior medical students would have to be called on to help out. They have been enthusiastic and faithful in attending. They are sincerely interested in trying to learn more about psychiatric problems and problems of mental behavior.

There is great interest in this type of treatment not only among medical students but among other people. Many other persons have asked whether they could attend some of these classes. That merely foreshadows Dr Yaskin's proposal to teach the principles of psychiatry in general education.

DR LOUIS H TWYEFFORT. Dr Hadden is proving to the future generation of medical practitioners the reality of psychosomatic factors. I should like to put in a plea for the use of such adjuvant methods of teaching as motion pictures in emphasizing the role played by emotional factors in many disturbed physiologic states. Such moving pictures could be put to good use in future teaching programs to make the coming physician aware of the physiologic reality of emotional factors, thus gradually overcoming the far too current concept that most psychosomatic symptoms are but figments of the imagination.

O Spurgeon English, M D , *Presiding*

*Regular Meeting, April 13, 1945*

**The Mentally Diseased Patient as an Individual** DR GEORGE S SPRAGUE

The stimulus for this paper was found in Freud's "Mourning and Melancholia," in which he said "Both scientifically and therapeutically, it would be fruitless to contradict the patient who brings these accusations against himself. He must surely be right in some way and be describing something that corresponds to what he thinks."

There are dangers involved in dealing with the psychiatric patient on the basis of diagnosis instead of insisting on learning his individual attitudes, reactions and symptoms. Generalizing, like a composite photograph, allows individual items to be lost sight of, to the detriment of the best management and understanding of the patient. Each person wants to be considered as an individual and is correct in prizing his personal differences. No matter what his symptoms, there are contained in them clues to a relationship of cause and effect which should be used to his advantage. The symptom is not the problem but, rather, the evidence that problems exist and should be sought out. But while psychiatry is interested as never before in subjective material, application of such progressive attitudes even yet lags behind awakening knowledge.

No two people are likely to build identical concepts for any of the familiar notions, such as death, love and politics, and if effort is not individually applied the patient may unwittingly be importantly misjudged and misunderstood. The result is a lowered effectiveness of therapy and a scientific loss in comprehension of the problems. In the period of postwar readjustments the challenge will be particularly urgent because of the numbers of returned service men who have difficulties in settling into the old situations and culture, while at the same time they have learned in service to look to psychiatry for help as never before.

DISCUSSION

DR ELEANOR KOCH I wish to express my appreciation of this paper and to welcome Dr Sprague to his practice of psychiatry in Philadelphia.

The emphasis which he places on the consideration of the patient as an individual is one which psychiatrists tend to take for granted as an "ABC" in practice. It is certainly that, but, although it is an emphasis to which they give ready lip service, a working use of all that is suggested in this paper requires continued and purposeful reiteration in its application to the practice of psychiatry.

I have thought of reasons for the difficulties the psychiatrist encounters in his attempts to individualize each patient's problems. Much of this tendency to categorize is related to the security value for the psychiatrist in the classified approach to a subject's difficulties. That his own sense of security should be obtained at the patient's expense is not compatible with good psychiatric practice.

DR PHILIP Q ROCHE I wish to express a word in praise of Dr Sprague for his stimulating paper and to convey to him a special word of appreciation for his directing our attention to the neglected field of criminal psychiatry. In this connection, Dr Sprague's comments on the uncritical use of rigid, diagnostic labels find particular application in dealing with patients whose behavior is disquieting. The tendency to regard people as diagnostic entities rather than as living persons is nowhere more persistent than in the treatment of delinquents. This is exemplified in the creation of figments of what people are fancied to be and in attempts afterward to squeeze them into such predetermined shapes. There come to mind such diagnostic terms as "defective delinquent," "moral imbecile," "psychopathic personality" and "constitutional psychopathic inferior."

I doubt the real usefulness of such terms in service to scientific aims. Some say they have value in the immediate practical expedients of penology, but

psychiatrists should always treat them with suspicion and be mindful of their corruptive effect. This is demonstrated too often in the use of these terms, which lend themselves to semantic distortion, to convey more of name calling than of understanding. Worse still, such terms creep into the law and petrify into sacred anachronisms. Such is the case of the present law, which has created a subspecies of monster called "defective delinquent." This brings to mind the admonition of Montaigne, "Through presumption they make laws for nature and marvel at the way nature ignores those laws."

DR SEYMOUR DAWITT LUDLUM. I am always intrigued by the fact that nobody ever raises the question of constitutional basis, that is, the physiologic constitutional basis.

DR GEORGE S. SPRAGUE. I appreciate the discussions of this subject. A statement made by Dr. Roche seems especially in point—that semantic problems are such a large part of this matter. An incident which will serve to illustrate this point occurred when a boyhood chum of mine was invited to spend a week on a friend's farm, where the friend had been contentedly spending the summer. But when the visitor came indoors with the remark, "Did you know that there is a quadruped on this farm?" the boy who lived there was for some while afraid to go outdoors any more. In a similar fashion psychiatrists are all prone to deal quite too predominantly with terms, rather than with the true facts about the patients and their problems.

#### Narcosynthesis of the Civilian Neurosis DR HERBERT FREED

With the aim of shortening psychotherapy in selected cases of neurosis, a technic somewhat similar to that which Grinker and Spiegel called narcosynthesis was utilized. The dynamic principle involved was that of mobilizing affects so that the emotional life of the patient would be reintegrated by fusing the idea with the feeling. It was felt that the barbiturates had a more or less specific effect not only in allaying anxiety but also in producing an affective state which allowed for a freer expression of erotic and aggressive drives. These could be utilized by the therapist in connection with the repressed memories and phantasies frequently obtained, as well as with previously known data.

Twelve patients were treated, of whom 4 had formal psychoanalytic therapy for periods up to a year and the others less intensive psychotherapy. Almost all the patients showed affective deviations prior to narcosynthesis, and their condition was described as schizoid, compulsive or detached.

The paper was a preliminary report. The patients had received from two to twelve treatments with narcosynthesis. The responses of the majority were considered promising.

#### DISCUSSION

DR LOUIS H. TWIEFFORT. Various workers giving barbiturates intravenously in narcosynthesis report the occasional occurrence of pulmonary edema, regardless of the quantity of drug used and sometimes in spite of the patients having reacted quite normally during previous treatments. The injection of atropine prior to treatment has been advised. What has been Dr. Freed's experience in this respect?

In what little experience I have had with narcosynthesis I have been impressed with the way in which it facilitates the expression of repressed aggression, which in many instances seems to be the chief determinant of the patient's anxiety.

DR HERBERT H. HERSKOVITZ. I should like to call the society's attention to the fact that Dr. Freed was one of the first to report results of insulin and metrazol shock therapy to this society. He is now the first to report on a method which is destined to become generally used in psychotherapy. Psychiatrists are always on the lookout for methods with which to shorten psychotherapy. However, one must be sure not to confuse a means with an end, a method with a therapy. Barbiturates serve no purpose other than to lessen repression, to bring

forth repressed memories and affects. Many would-be psychotherapists will, if this fact is not sufficiently understood, talk glibly of giving "sodium amytal treatments" or "sodium pentothal treatments." The barbiturates themselves have no therapeutic effect. They merely weaken repression and thus are an aid to psychotherapy. I should like to stress my conviction that therapeutic success is due not to the drug but to the therapist. I do not think the barbiturates produce a state of euphoria any more than alcohol or other drugs can produce aggression or euphoria. By lessening inhibition, by weakening repression, the patient's underlying tendencies are brought out. I cannot believe that there is a definite chemical reaction on certain areas of the brain produced by the barbiturates which causes a feeling of well-being. I wonder whether the feeling of well-being, described by Dr. Freed and others, is not caused by a release of tension and by the allaying of anxiety.

One hears more and more of treatments such as narcohypnosis, narcosynthesis, narcoanalysis and others. I hope that with the intravenous administration of barbiturates there will not be built up a confusing array of terms, all of which mean the same thing, psychotherapy.

DR H. CRAIG BELL. Dr. Freed's presentation has definite psychotherapeutic value in a limited field. I should like to ask him two questions. How long does he find it necessary to keep a patient under observation after such procedure? Has he had any patients who have been very refractory to the drug?

I have never seen any cases of pulmonary edema. How often do patients show such reactions as vomiting? I have used this type of therapy with schizophrenic patients, without any results, and the patient showed no emotional changes.

In my experience, I find that the patients tend to be euphoric after treatment and feel decidedly better.

DR ROBERT S. BOOKHAMMER. Dr. Freed's approach to the use of chemohypnosis seems to me to be sound in that he recognizes the need to do more than merely have the patient abreact emotional experiences while under the influence of the drug. My own experience with patients who have had this treatment for a civilian neurosis has been that emotional abreaction without subsequent use of the material produced under narcosis may be even harmful. The resistance, only temporarily circumvented by barbiturates, remains as a problem the patient must deal with consciously, and it is the duty of the therapist to aid him in this task by going over with him in all its implications the meaning of whatever material has been produced by this method.

DR HERBERT FREED. I want to thank the discussers for their kind and interesting remarks.

Dr. Twyeffort made a comment about the use of atropine. I have not had the unfortunate experience with pulmonary edema and perhaps I am careless. As I think of the dangers of pulmonary edema and how I treated it in insulin shock therapy, it makes me feel that I shall do more about it in the future.

Dr. Twyeffort brought out something which I tried to emphasize, that is, the hostility that comes out in these patients. One of the patients which he described had an anxiety state. Treatment brought out hostility, but she went into a state in which she required prolonged narcosis. I think that one should allow such a patient to bring out material within the limit of her anxiety tolerance by experimenting with the dosage. As to refractoriness to the drug, patients with a great deal of anxiety or alcoholic patients can be given up to 15 grains (0.975 Gm.) without securing much effect. This is especially true of alcoholic patients.

Dr. Herskovitz pointed out something with which I agree for the most part, but not completely. I do not think the action is simply a matter of lessening repression. I feel that barbiturates have a specific effect. In my experience, practically every patient given barbiturates showed euphoria at some stage. I have not given alcohol to patients as a substitute for the barbiturates. Dr. Thorner, of this society, has administered alcohol by tube. Some have even

given it intravenously and claimed that it produced the same effects as sodium amytal. My feeling is that barbiturates produce a change which is different from that produced in hypnosis.

In answer to Dr. Bell's question as to how long after such a procedure one can let the patient leave, I think that once the proper dose of sodium pentothal has been achieved the patient can walk out in ten or fifteen minutes after treatment. Until one reaches the proper dose, one may have to let him lie down for a short time after treatment.

Dr. Bookhamner stresses a point which I was trying to emphasize. The important aspect in this treatment is not the giving of a drug but the knowing what to do with the material obtained. In order to get the patient to accept this material consciously, I have felt that a procedure should be used which I have experimented with only a little but hope to do more with in the near future, that is, to make a phonograph record during the treatment and then play it back to the patient afterward. I think such records would be extremely beneficial in treatment of the patient as well as for teaching purposes.

#### Memorial to Dr. Henry I. Klopp. DR. ARTHUR P. NOYES, Norristown, Pa.

Dr. Henry I. Klopp, long a respected member of this society, died on March 15, 1945. Dr. Klopp was born in Lebanon County, Pa., Jan. 1, 1870. He was educated in the public schools of that county and at Palatine College, Myers-town, Pa. He graduated from Hahnemann Medical College in 1894 and from 1895 to 1912 was on the staff of the Westboro (Mass.) State Hospital. In that year he became superintendent of the newly constructed Allentown (Pa.) State Hospital, a position which he held until his retirement, July 1, 1942.

Dr. Klopp contributed his services and sound judgment to many welfare agencies. A genial and friendly person, he was much beloved by his professional associates and to a remarkable degree enjoyed the confidence and respect of the community and of its organized social and welfare agencies. Taftful but courageous in public work, he was uncompromising in what he believed to be for the interests of his patients and the hospital with which he was connected. Vigorous and methodical, Dr. Klopp impressed his personality on the hospital for the development and growth of which he was responsible. Under his guidance the Allentown State Hospital became in many respects the outstanding one in the Pennsylvania mental hospital system. His career was one of outstanding service in public psychiatric work, the results of which will long do him honor.

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#### CHICAGO NEUROLOGICAL SOCIETY

Ralph C. Hamill, M.D., *President, in the Chair*

*Annual Meeting, May 8, 1945*

**Presidential Address: Learning and Belief.** DR. RALPH C. HAMILL

**Chronic Leptomenigeal Thickening Following Treatment of Meningitis with Sulfonamide Drugs.** DR. PERCIVAL BAILEY

This paper was published in the December 1945 issue of the *Annals of Surgery*, page 917.

**Penicillin Therapy for Spina Bifida.** DR. A. EARL WALKER and DR. HERBERT C. JOHNSON

One of the most difficult problems for the neurosurgeon is the management of infected meningoceles and meningomyeloceles. Two infants with infected meningomyelocele were treated with intrathecal injections of penicillin, with resulting elimination of the infection and conversion of the saccular meningomyelocele into a small, completely epithelialized scar.

The mortality rate for the usual conservative or operative treatment of infants with spina bifida and meningocele or meningomyelocele is high. A method of medical management which would materially decrease this mortality offers a means by which the patient may be tided over for a few years, until the neurologic defect and the danger of hydrocephalus may be evaluated more accurately. It is probable that the routine use of penicillin in cases of infected or potentially infected lesions of spina bifida, especially those which are not covered with normal skin, would permit healing of the meningeal sac with a firm scar. The administration of penicillin intrathecally in daily doses of 10,000 Oxford units in 2 to 3 cc of isotonic solution of sodium chloride would appear to be the optimum method of therapy and to invoke little reaction.

The fact that a simple, safe method is available for the treatment of infected or potentially infected lesions of spina bifida should not lead to overindulgence in its use in those cases of meningomyelocele and myelocele associated with a serious neurologic defect. If the paralysis is obviously so severe that the patient cannot develop into a socially acceptable person, the administration of penicillin, although it may allow the spinal defect to heal, is contraindicated both on sociologic and on economic grounds. It seems unlikely that the use of penicillin in selected cases of spina bifida will introduce social problems.

#### DISCUSSION

DR PAUL C BUCY: The treatment of spina bifida is a problem which has concerned me for a number of years. I should like to stress the point made in the latter part of the paper. In dealing with cases in which there is a neurologic defect I have never regretted having withheld treatment, but on several occasions I have regretted treating these severely deformed infants. I believe it is unwise to treat any child with meningocele who has a severe incapacitating neurologic deficit with any method that has any likelihood of success. One of the greatest medical tragedies is to have such a child survive for many years with paralyzed, anesthetic legs and absence of control over the bowel and bladder.

DR HERBERT C JOHNSON: Dr Walker has done considerable work on penicillin and its convulsive effect on the central nervous system. Early in the investigation the question was raised whether the convulsive factor was due to impurities or was inherent in the penicillin itself. With a number of methods, attempts were made to separate the convulsive factor from the antibiotic factor. In almost all experiments, however, it was found that when the antibiotic factor was destroyed to a certain degree the convulsive factor was proportionately diminished in potency.

A definite answer to the statement that the convulsive activity of penicillin is due to impurities can now be made, since recently we obtained an amount of pure crystalline sodium penicillin. Experiments have shown that pure penicillin is just as potent in producing convulsions as is commercial penicillin. It is apparent, then, that the convulsive activity of penicillin is not due to impurities present in the commercial product.



## News and Comment

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### THE AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY, INC

The following candidates were certified at a meeting of the board in Chicago, May 24 and 25, 1946

*Psychiatry*—By Examination Samuel E Abel, Murfreesboro, Tenn, James A Alston, Providence, R I, Florence O Austin Patton, Calif, Julius Barasch, Wingdale, N Y, Major Frank R Barta, MC, AUS (formerly New Haven, Conn), Leo Henry Bartemeier, Detroit, Charles R I Beall, Atlanta, Ga, Robert W Beck, Milwaukee, Adair D Bedinger, Providence, R I, Ivan C Berlien, Detroit, H Robert Blank, Brentwood, N Y, Melvin F Blaurock, Oak Park, Ill, Charles A Bohnengel, Moorstown, N Y, Major William W Bourke, MC, AUS, John D Bradley, Durham, N C, Lieut Col Charles A Brown, MC, AUS, William Brown, New York, Byron S Cane, Washington, D C, Walter A Carley, St Paul, Minn, R Charman Carroll, Durham, N C, Jesse F Casey, Topeka, Kan, Major Louis A Cibelli, MC AUS (formerly Roanoke, Va), Louis F Cleary, Baltimore, Jules V Coleman, Denver, Henry H Crank, Topeka, Kan, Lieut Col J O Crownwell, MC, AUS (formerly Blackfoot, Idaho), Capt Leon S Diamond MC, AUS (formerly American Lake, Wash), Clifford O Erickson, Rochester, Minn, Benjamin Erps Downey, Ill, \* Harrison S Evans, Columbus, Ohio, Capt Edward G Feldman, MC, USA (formerly Columbus, Ohio), Raymond Fellman, Chicago, Robert H Felix, Washington, D C, Major Lewis J Fielding, MC, AUS (formerly Waco, Texas), William S Fife, Royal Oak, Mich, William A Florio, Washington, D C, Capt Irving A Gail, MC, AUS (formerly Lexington, Ky), Robert W Gans, Memphis, Tenn, Mark Gerstle Jr, New York, Merton M Gill, Topeka, Kan, Fritz Glaser, Cleveland, Benjamin H Gottesfeld, Hartford, Conn, Charles C Graves Jr, Marlboro, N J, Burton P Grimes, St Peter, Minn, Robert Gronner, Chicago, Walter M Gysin, Omaha, William L Harris, Kings Park, N Y, Paul Haun, Washington, D C, James R Hawkins, Cincinnati Capt J Lester Henderson, MC, AUS (formerly Pasadena, Calif), Charles K Hepburn, Indianapolis, Thomas V Hoagland, Ypsilanti, Mich, Capt Morris Isenberg, MC, AUS (formerly Cheyenne Agency, S D), Valeria R Juracek, Ann Arbor, Mich, Benjamin H Kagwa, Chicago, Paul Kells, Miami, Fla, Capt Albert Kraus, MC, AUS (formerly Chillicothe, Ohio), Othilda Krug-Brady, Cincinnati, Edward E Landis, Louisville, Ky, Charles E Leonard, Oklahoma City, Harold N Levine, Woodside, N Y, Anne G Livingston, Waltham, Mass, David Levitin, Chicago, Theodore Lidz, Baltimore, James V Lowry, Lexington, Ky, Lieut Col Henry Ludens, MC, AUS (formerly Cleveland), Major Norman C Mace, MC, AUS (formerly American Lake, Wash), Capt Aaron W Mallin, MC, AUS (formerly Northport, N Y), Ben Marks, Detroit, Major Aaron S Mason, MC, AUS (formerly Downey, Ill), Robert L Meller, Minneapolis, Brig Gen William C Menninger, MC, AUS (formerly Topeka, Kan), \*Lieut Herman A Meyersburg, (MC) USN (formerly Charlottesville, Va), Donald F Moore, Ypsilanti, Mich, Donald P Morris, Dallas, Texas,

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\* The asterisk denotes complementary certification

Raymond J Norfray, Chicago, Jacob P Norman, Foxboro, Mass, Douglas W Orr, Seattle, Col Ernest H Parsons, M C, A U S (formerly Washington, D C), Samuel Paster, Memphis, Tenn, Stanley Peal, Towson, Md, Frank P Pignataro, Marlboro, N J, William W Pike, Orangeburg, N Y, Major Simon Polan, M C, A U S (formerly Philadelphia), Isidore Portnoy, New York, Edward S Post, Marion, Ind, Jack Rapoport, New York, James E Rappa, Brooklyn, Donald R Reader, Fort Snelling, Minn, Major Lewis L Robbins, M C, A U S (formerly Topeka, Kan), Isadore Rodis, Washington, D C, Capt Samuel R Rosen, M C, A U S (formerly Brooklyn), Ernst Schmidhofer, Chicago, Laurence A Senseman, Saylesville, R I, Melvin Simonson, Downey, Ill, Lieut Col Beverley E Smith, M C, A U S (formerly Washington, D C), Capt Manuel Straker (formerly London, Ontario, Canada), Joseph D Sullivan, New York, Major George F Sutherland, M C, A U S (formerly Belmont, Mass), Virginia S Tarlow, Chicago, Lieut Col Joseph C Tatum, M C, A U S (formerly Washington, D C), Oreon K Timm, Fort Custer, Mich, John D Trawick Jr, Bethesda, Md, Chester Wade, Oconomowoc, Wis, Julius M Wallner, Ann Arbor, Mich, Joseph Walzer, New York, William Weisdorf, Chicago, C A Whitaker, Oak Ridge, Tenn

*Neurology*—By Examination John L Garvey, Milwaukee, Heinz Kohut, Chicago, Vasilios S Lambros, Washington, D C, William H Sweet, Boston, Joseph Zimmerman, Brooklyn

*Psychiatry and Neurology*—By Examination Daniel W Badal, Cleveland, Joe R Brown, Minneapolis, Rawley E Chambers, Denver, Major Walter L Ford, M C, A U S (formerly St Louis), Bernard R Goldberg, Newark, N J, Robert H Groh, Washington, D C, Capt Avraam T Kazan, M C, A U S (formerly New York), Henry D Lederer, Cleveland, Louis Linn, New York, Robert J Mueller, St Louis, Julius L Rosenbloom, Pueblo, Colo, Isadore Spark, Philadelphia, Walker Thompson, New Orleans, Henry D Von Witzleben, Chicago, Cornelia B Wilbur, New York, Joseph M Zucker, Providence, R I

*Psychiatry*—On Record William M Bevis, St Petersburg, Fla, Clarence G Cox, Milledgeville, Ga, William M Dobson, Northampton, Mass, C L Fessenden, Kings Park, N Y, E Moore Fisher, Washington, D C, John A Holland, Cleveland, James P Kelleher, Rome, N Y, Marion R King, Washington, D C, Edwin M Levy, Canandaigua, N Y, Mary MacLachlan, Kings Park, N Y, Clarence R Miller, Coatesville, Pa, Major Henry S Mitchell, M C, A U S (formerly Baltimore), Erwin H Mudge, Helmuth, N Y, Appleton H Pierce, Philadelphia, Philip J Trentzsch, New York, John L Van de Mark, Rochester, N Y

*Psychiatry and Neurology*—On Record Winthrop Adams, Boston, Adelpfar A Marsteller, Washington, D C, Leonard Ravitz, Cleveland, Julius Sobin, Newark, N J

#### REFRESHER COURSE IN PSYCHIATRY, UNIVERSITY OF CALIFORNIA

The University Extension, University of California, in cooperation with the Division of Psychiatry, University of California Medical School, announces a twelve weeks' refresher course in psychiatry and neurology, starting Monday, Sept 16, 1946, at the Langley Porter Clinic, University of California Medical School

This course is a repetition of the course in psychiatry and neurology offered in January, February and March 1945, with minor changes. It is open to physicians generally, particularly to those returning from the armed forces. Registration is tentatively limited to sixty physicians, and the University of California reserves the right to give preference to its own graduates and to veteran physicians.

Instruction will be given under the direction of Dr. K. M. Bowman, professor of psychiatry, University of California Medical School, with the assistance of staff members from the various divisions of the medical school.

Registration is open to graduates of approved medical schools with nine months' general internship. Immediate application for registration is recommended. It should contain the following information: (1) place of legal residence, (2) medical school attended and date of graduation, (3) experience and training in psychiatry and (4) short record of military service. Applications should be addressed to Stacy R. Mettler, M.D., head of postgraduate instruction, Medical Center, University of California, San Francisco 22.

The fee for the course will be \$200, payable in advance. Candidates registered under the provisions of the G. I. Bill of Rights will receive a refund, prorated according to their terminal leave. Enrollment fee should be either enclosed in letter or mailed immediately, with check or money order payable to the Regents of the University of California (for "Course in Psychiatry").

Further details regarding this course may be obtained from the Langley Porter Clinic, Overland 8080, or from the office of Dr. Mettler, Montrose 3600, Local 255 (secretary).

#### FELLOWSHIPS FOR TRAINING IN CHILD GUIDANCE CLINIC PSYCHIATRY

The National Committee for Mental Hygiene, Inc., offers fellowships for training in child guidance clinic psychiatry. The training is for positions in community clinics where psychiatrists, psychologists, social workers and others collaborate in the treatment of children suffering from emotional or mental illness.

Some of the fellowships are for two years, some for one year. The stipend is from \$2,600 to \$3,000 for the first year and more for the second year. Prerequisites are graduation from an approved medical school, a general internship and two years of general psychiatry. Military psychiatry will be accepted for at least a part of the two years.

Opportunity is provided for the fellow to develop his own skills in a well organized service, with the support of a carefully planned training program and adequate supervision. The training centers are selected on the basis of standards which have been established by the National Association of Child Guidance Clinics.

For further information write to Dr. Milton E. Kirkpatrick, Director, Division on Community Clinics, the National Committee for Mental Hygiene, Inc., 1790 Broadway, New York 19.

## Obituaries

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WALTER EDWARD DANDY, M D

1886-1945

Walter Dandy is dead To those who knew his abundant vitality and driving energy, and his forcefulness, even in recent days, in presenting his views and convictions, Dandy has been so vital a person that it is difficult to believe that his voice will no longer be heard He died as a result of coronary thrombosis, suddenly, on April 19, 1946 He leaves a son, Walter, who is in medical school, three daughters, Mary, Kathleen and Margaret, and his wife, Sadie Martin, whom he married in 1924

Born in Sedalia, Mo , April 6, 1886, of parents from England and North Ireland, Walter Edward Dandy attended the public schools of Sedalia and the University of Missouri and entered the Johns Hopkins University School of Medicine in 1907, with advanced standing He graduated with the degree of Doctor of Medicine in 1910 and continued his work in this medical school and hospital, rising through the various stages of the surgical service and academic rank, to become adjunct professor of neurological surgery in 1932

Within three years after receiving the M D degree he had, with characteristic energy and industry, completed and published three scientific studies, one on the youngest human embryo which had been studied up to that time, one on the blood supply of the pituitary body and one on the nerve supply of this intracranial structure His classic work, "An Experimental and Clinical Study of Internal Hydrocephalus" (*J A M A* 6:2216 [Dec 20] 1913), was published in 1913, when he was 27 years old Five years later he produced another classic, on pneumoventriculography (*Ann Surg* 68:5-11, 1918), a procedure which he originated and which has been very valuable in the precise localization of intracranial lesions It has repeatedly been said that ventriculography has been the greatest single contribution to brain surgery ever made

Dandy's mastery of neurosurgical technic enabled him to make a brilliant series of technical contributions, impressive even in the form of a partial list operations for the complete removal of acoustic neuromas, radical new operations for trigeminal neuralgias and neuralgias of other cranial nerves, and operations for torticollis and

for Menière's disease. His characteristic combination of care in procedure and boldness of aim was well exhibited in his operations for the removal of congenital aneurysms of the arteries forming the circle of Willis and of their large branches. Again, his self-confident independence of judgment and his virtuosity in surgical technic were demonstrated in his operations for ruptured intervertebral disks, a condition which he discovered and reported in 1929.

Much of Dandy's success in making discoveries and innovations was made possible by his courage and independence of judgment, but boldness was by no means the only or principal virtue of his work. His improvement in the surgical treatment of cerebral abscess by utilizing aspirations through tiny trephine openings in the skull was an example of the value he placed on conservative technic.

Dr. Dandy was a member of the American Surgical Association, the American Neurological Association, the Southern Medical Association, the Southern Surgical Association, the American Medical Association, Phi Beta Kappa and Sigma Xi.

In addition to his scientific reports in journals, portions of Dandy's large experience were published in a series of books, among which are "Benign Tumors of the Third Ventricle, Their Diagnosis and Treatment," Springfield, Ill., Charles C. Thomas, Publisher, 1933, "Benign, Encapsulated Tumors in the Lateral Ventricles of the Brain, Diagnosis and Treatment," Baltimore, Williams and Wilkins Company, 1934, "Orbital Tumors," New York, Oskar Piest, 1941, "Intracranial Arterial Aneurysms," Ithaca, N. Y., Comstock Publishing Co., Inc., 1944.

Besides his direct contributions to neurosurgery, Dandy has inspired by his example a series of brilliant younger neurosurgeons, who worked with him and through whose work he will continue to be a living force for further advancement.

The outstanding clarity and succinctness of Dandy's papers were the expression of a forthright habit of mind, which sometimes also involved him in stormy controversies and a few personal enmities, but he regularly emerged from such disputes with the increased respect of his scientific colleagues, and it can be safely predicted that his stature as a great figure in medicine will grow in the perspective of time. His international reputation brought him large numbers of patients, and he did a tremendous amount of work. Simple and unpretentious in manner, generous in many unpublicized ways and simple in his personal tastes, he was a delightful friend and companion. There is much personal sorrow at his death, as well as regret at the cessation of a brilliant career of investigation and service for the relief of human suffering.

JOHN C. WHITEHORN, M.D.

## LADISLAV HAŠKOVEC, M D

1866-1944

Ladislav Haškovec, professor ordinarius of neurology and psychiatry in Prague since 1919, died during the German occupation of Czechoslovakia, on Jan 16, 1944

Ladislav Haškovec was the founder of Czechoslovakian neurology, which he separated from and made independent of internal medicine. He was a pupil of the famous French neurologists Charcot and Gley, and his publications and papers showed the ingeniousness and brilliancy of the French school of neurology. He wrote more than two hundred scientific publications in various fields of neurology, neurohistopathology, psychiatry, endocrinology, eugenics and mental hygiene. The most outstanding and fundamental publications were devoted to akathisia, pilomotor reflex, histopathologic observations in cases of paralysis agitans, localization of the center for consciousness, activity of the thyroid and parathyroid gland, infantile speech in adults, traumatic and vegetative neuroses, contractures and tremor.

For over thirty years he published and edited the Czechoslovakian journal *Revue v neuropsychopathologi*. He was a member of numerous medical societies and institutions all over the world. In 1930 he was nominated chairman of the First International Congress of Mental Hygiene, in New York, and in 1935, vice president of the Second International Congress of Neurologists, in London.

Ladislav Haškovec will be remembered by his friends and pupils as a noble and generous man, and his death is a loss to his country as well as to neurology, which he enriched by many original and interesting contributions.

JOSEPH A. WINN, M D

## CORRECTION

In the article by Dr Robert Wartenberg entitled "Associated Movements in the Oculomotor and Facial Muscles," in the May issue (ARCH NEUROL & PSYCHIAT 55:439, 1946) it is stated "the gastrolacrimal reflex, and the auriculotemporal syndrome are not uncommon but, oddly enough, are not even mentioned in such a detailed work as Wilson's<sup>1</sup> Neurology." This is not correct. Wilson, on page 379 (Neurology, London, Edward Arnold & Co, 1940), under "trigeminal nerve," does mention the auriculotemporal syndrome. Concerning the gustolacrimal reflex he says, under facial nerve (page 403) "Lachrymation develops at times during facial overaction e.g., in the process of eating."

## Book Reviews

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**What People Are** By Clark W Heath, M D, in collaboration with others  
Price, \$2 Pp 137 Cambridge, Mass Harvard University Press, 1945

To describe rather than to define, a normal young man, two psychiatrists, an internist, a physiologist, a physical anthropologist, a psychologist and a personnel worker, under the auspices of the Grant Foundation, have been accumulating data for the past six years. The initial report of their study is presented by one of them, Clark W Heath, in this small, lucid volume.

The Grant Study is an institution which was established in 1938 at Harvard University for the study of normal persons, its aims are to find, relate and explain the characteristics of healthy young men and to seek methods and gain wisdom which will direct people to suitable training and careers and help them live happier, more successful lives.

An arbitrary concept of normal as "balanced" is first stated, then automatically defined by the method of selection of the young men. For this work, college sophomores were selected as the best available group, and only those were studied who were doing satisfactory work and whose "adjustment" was at least average. In a series of personal interviews, the frequency and technique of which are described, the investigators mentioned use eight different disciplines or methods of study: measurement of soundness, outstanding personality traits, adjustment (environmental and intrapersonal) and socioeconomic, morphologic, physiologic, medical and mental status. An interesting descriptive analysis of these disciplines makes up the bulk of this report. Integration of observations with the different disciplines is also presented.

The material is interesting for itself, but more noteworthy are the constant reminders, both stated and implied, that the work is just a tiny beginning, an infinitesimal portion of a field for observation which is vast, complex and substantially unexplored.

Questions must inevitably arise in the mind of any reader as to the criteria for selection of subjects for study or the objectivity of the interviewers. One may object to the tendency to imply desirability or goodness to certain of the character traits, always from the standpoint of career guidance and social adaptation. Or one may object to the use of terms such as "sound," "healthy" or "well integrated." But the modesty with which the author states the scope of the report indicates simply that further and enlarged studies are needed, not that this small beginning is a poor one.

Many more people from all walks of life must be investigated by representatives of more and varied disciplines before conclusions can be formulated, common denominators found or a decision made as to whether the study of normal persons can be sufficiently resolved as to be worth while. This volume offers each reader a point of departure for ideas for further study according to his own special interest.

**Klinische und erbbiologische Untersuchungen über die Heredoataxien** By  
T Sjogren Acta psychiatrica et neurologica, supplement 27 Price, 15 kroner.  
Pp 200, with 25 tables Copenhagen Einar Munksgaard, 1943

Sjogren has long been known to students of heredity in relation to neurologic disorders, having had abundant opportunities for genetic investigations in the relatively stationary population of Sweden. His industry in the assembling of data in the present large investigation is noteworthy, and his mathematical handling of the material is commendable, if somewhat beyond the scope of the average neu-

rologist This volume comprises a study of 188 cases of the heredoataxias, occurring in 118 families, and investigations covering a total of 3,111 persons Cases occurring in family groups are reported, and maps are appended to show the geographic relationships The present observations are not so striking as were those in the author's previous studies on Huntington's chorea, in which parish records indicated the inheritance of the disease through as many as nine generations In the present investigation the disease was traceable through five generations From his study, in which records were available over several decades, the author concludes that definite mental deterioration takes place in the end stages of both Friedreich's disease (hereditary spinal sclerosis) and Marie's heredoataxia (hereditary cerebellar ataxia) and, furthermore, that muscular atrophy occurs late in the disease in many cases The average age of onset of Friedreich's ataxia is  $13 \pm 07$  years, while that for Marie's ataxia is  $34 \pm 19$  years and that for a heterogeneous group is  $50 \pm 23$  years The age at which the disease develops is determined by the family, the similarity of age being especially noticeable in siblings The author's fourth type of the disease, *forme fruste*, shows little tendency to progression and is not accompanied with dementia or muscular atrophy, although there may be a positive Babinski sign, loss of reflexes and the telltale Friedreich's foot

Genetic analysis shows that Friedreich's ataxia is a recessive monohybrid, whereas Marie's ataxia is overwhelmingly a dominant monohybrid, from the genetic standpoint, therefore, these two diseases are different The heterozygotes seem to occur in small groups in various parts of the country The material was too small for investigation of twins

Sjogren's study is a solid contribution to genetics as related to neurologic disorders, it is well documented and beautifully printed

**The Psychiatric Novels of Oliver Wendell Holmes** Abridgment, Introduction and Annotations By Clarence P Oberndorf Price, \$3 Pp 268 New York Columbia University Press, 1943

Oberndorf has undertaken to dissect, condense and explain the three novels of Holmes that deal especially with psychologic problems, namely, "Elsie Venner," "The Guardian Angel" and "A Mortal Antipathy" Each of these novels presents a hero or a heroine whose adjustment has been warped by circumstances, and, while a "cure" is forthcoming in the last two, Elsie Venner went to her death in what might be considered a catatonic episode The "cures" savor somewhat of shock, since an overturned boat in Myrtle Hazard's case and a fire in the home of Maurice Kirkwood, with the attendant circumstances, resulted in progressive readaptation Holmes's novels are old-fashioned, with their dialogue, their dissertations by various characters and the rather cumbersome working out of the plots There is, however, a certain felicity of expression that Oberndorf has retained, so that the essentials of each story stand out in strong relief "Many of the passages which my pencil underscored," he writes, "were so anticipatory and far-sighted, so cogent and valid in psychiatric thought today that I could not refrain from making comments upon them here and there"

This procedure has resulted in a series of notes which detract from the stories The annotations are superficial, anecdotal and patronizing After all, Holmes was not the immediate precursor of Freud, nor did he live in a world of barrenness as far as psychologic motivation was concerned The Boston of Holmes's era was alive with querying in the psychologic sphere, and, while the conservative element among Holmes's professional brethren may not have been acutely aware of the theories propounded, P P Quimby and Mary Baker Eddy remain as landmarks in psychotherapeutic thought Oberndorf regards Holmes as a gifted amateur, apparently, and damns with faint praise when he compares him with the master, Freud



**Mental Changes After Excision of Cerebral Tissue A Clinical Study of 16 Cases of Resections in the Parietal, Temporal, and Occipital Lobes**  
By G Rylander *Aeta psychiatrica et neurologica*, supplement 25 Price, 12 kroner Pp 81 Copenhagen, Einar Munksgaard, 1943

This is a companion piece to the study, published in 1939, dealing with mental changes after resection of the frontal lobes in 32 cases of tumor. In the present study, Rylander has employed the same methods of examination, controlling each observation by similar studies on a member of the family or a close associate and then applying statistical methods to determine the differences. Each patient was given a standard intelligence test, and various other tests which had revealed characteristic differences in the frontal lobe series were used. Rylander points out that none of his patients showed significant losses in intellectual performance as long as the centers of the intellectual machinery (speech, gnosis) were essentially undamaged. Furthermore, none of his patients showed euphoria, restlessness or silliness, and most of them were reported to be of the same temperament after operation as before development of the symptoms of tumor. Most of the patients exhibited some falling off in endurance, some loss of memory and slight irritability, and these alterations can probably be explained by the general reduction in brain mass. Difficulties met with because of impaired vision and epileptic seizures, however, caused a gloomy personal outlook in some cases.

The author points out that extensive resections may be undertaken in the parietal, temporal and occipital lobes without damaging the capacity of the patient as long as the language centers are uninvolved. This statement contrasts strongly, however, with his observations on resection of the frontal lobes, a procedure which involves "the risk of mental invalidism in patients doing mental or other complicated work."

Rylander has given an excellent picture of the integrity of the personality when the posterior portions of the brain are attacked, and he thereby points out the specific qualities in the personality that are impaired after resection of the frontal lobe. In view of the increasing interest in the subject of psychosurgery, these monographs by one of Sweden's foremost investigators should be studied with care. The author points to the necessity of carefully controlled observations, with pre-operative and postoperative tests by the same investigator, who should also be present at the operation in order to ascertain the exact portion of the brain removed. "The method is laborious, but it should yield results with a sound background of reality."

## COURSE AND RATE OF REGENERATION OF MOTOR FIBERS FOLLOWING LESIONS OF THE RADIAL NERVE

SYDNEY SUNDERLAND, M.D., D.Sc.  
MELBOURNE, AUSTRALIA

THE OBJECT of this paper is to record and to discuss the significance of observations on the course and rate of regeneration of motor fibers following complete interruption of conduction in the radial nerve due to gunshot wounds, simple fractures of the humerus, penetrating injuries and lacerations. The results of an investigation of simple compression injuries of this nerve have already been described (Sunderland<sup>1</sup>).

Detailed observations on motor recovery have been reported by Stopford<sup>2</sup> and by Seddon, Medawar and Smith<sup>3</sup>. Reference will be made to the results of their studies in the appropriate sections of the text.

In the present investigation of a series of 63 lesions of the radial nerve particular attention was paid to the following points:

1. End results
2. Course of spontaneous regeneration and the regeneration following suture
3. Pathologic features of the lesion, as deduced from a study of the course of regeneration
4. Selection of cases suitable for investigation of the rate of regeneration of peripheral nerves in man
5. Rate of regeneration, which was estimated over different segments of the nerve in order to determine whether regeneration progresses at a uniform rate or otherwise

From the Department of Anatomy and Histology, University of Melbourne, Australia

1. Sunderland, S. Traumatic Injuries of Peripheral Nerves. I. Simple Compression Injuries of the Radial Nerve, *Brain* 68: 56-72, 1945

2. Stopford, J. S. B. The Results of Secondary Suture of Peripheral Nerves, *Brain* 43: 1-25, 1920

3. Seddon, H. J., Medawar, P. B., and Smith, H. Rate of Regeneration of Peripheral Nerves in Man, *J. Physiol.* 102: 191-215, 1943

6 Composition and duration of the interval between the time of the injury and the onset of recovery and the influence of this interval on the course of regeneration subsequent to the latter

7 Maximal latent period subsequent to the injury after which spontaneous regeneration may still occur and proceed to completion

#### MATERIAL AND METHOD OF INVESTIGATION

The observations are based on a group of 63 cases of lesions of the radial nerve occurring in a series of 301 consecutive cases of peripheral nerve injuries which were personally studied over the period of 1941 to 1945 at the One-Hundred and Fifteenth Australian General Hospital and the Repatriation Clinic, Melbourne, Australia. The case histories and the end results in these 63 cases are to be reported in considerable detail elsewhere. Only 31 of these cases were suitable for the purposes of the present study, which demanded that interruption of conduction in the nerve should be complete when the patient first came under observation and that examinations should subsequently be made at regular and frequent intervals in order to obtain information which would enable one to ascertain, with reasonable accuracy, the time and order of motor recovery in individual muscles.

Throughout the text cases have been referred to by serial number only (personal series), and reference should be made to table 2 for information concerning the injury responsible for each nerve lesion and the level of the lesion above the lateral epicondyle of the humerus.

To make possible a comparison of the observations and results in this series with those obtained by other investigators, it is proposed, before proceeding to the discussion, to define and specify the exact meaning ascribed to certain terms employed in this report.

*Initial Delay*—The interval between the injury and the time when regenerating axons enter the distal segment is termed the initial delay.

*Latent Period*—The interval between the injury and the onset of recovery is termed the latent period.

*Infection and Scarring*—An attempt was made in each case to assess the degree of infection and local scarring about the nerve in order to determine the influence of these factors on the course of regeneration. This was obviously difficult, and only the simplest classification into "significant" and "insignificant" was attempted.

The degree of infection was assessed on the basis of general symptoms, culture of material from the wound, presence or absence of osteomyelitis, period during which the wound discharged, time taken for the wound to heal and extent of residual scarring.

The degree of scarring was estimated on the extent of injury to soft tissue and on the area and character of the residual scar and whether this was adherent, free, depressed or otherwise.

*Motor Recovery*—In studying motor recovery particular attention was directed to the onset of contraction in the brachioradialis, extensor carpi radialis longus, extensor digitorum communis, extensor carpi ulnaris, abductor pollicis longus and extensor pollicis longus muscles. No attempt was made when examining muscular function to separate the respective muscles of the extensor carpi radialis group, the abductor pollicis longus from the extensor pollicis brevis or the segment of the extensor digitorum communis to the index finger from the extensor

*indicus proprius* The members of each group have substantially the same actions and are so closely associated anatomically that it is often impossible to decide with absolute certainty by palpation when one is contracting and the other is not

A study of the metric and nonmetric features of the motor branches of the radial nerve in 20 specimens revealed that the shortest distance to the extensor carpi radialis longus as measured from a fixed point along the nerve and its branches was invariably shorter than that to the extensor carpi radialis brevis The first contractions in this combined mass could therefore be attributed to the former provided the regenerating axons to each muscle grow at the same rate and commence to do so at the same time

In no instance were the shortest fibers to the extensor *indicus proprius* shorter than those to the extensor digitorum communis In 4 specimens the extensor digiti quinti proprius preceded the extensor digitorum communis in the order of innervation, though in only 2 of these was the difference between their lengths significant Consequently, the extensor digitorum communis may, as a rule, be expected to recover before the other two muscles, and its action should not be attributed to them

In every specimen the distance to the abductor pollicis longus was shorter than that to the extensor pollicis brevis, and therefore in cases of uncomplicated recovery the first signs of returning function should be attributed to the former

Palpable contraction of the muscle, or movement which was undoubtedly attributable to its action alone, was the criterion adopted for detecting returning function, and in this connection due regard was paid to the possibility of transmitted contraction and trick movements One source of error, however, remains It has been found that electrical stimulation of a nerve at operation may produce a response in a muscle before the appearance of voluntary contraction This indicates that reinnervation of a muscle and its ability to contract voluntarily do not necessarily return simultaneously Case 231, in the group of gunshot wounds associated with fractures of the humerus, will illustrate this point The radial nerve, which had originally been reported as completely severed, was explored twenty-six weeks after the injury, when infection had subsided It was exposed in the middle and distal thirds of the arm and appeared normal in every respect Direct and strong stimulation of the nerve resulted in a flicker of contraction in some of the fibers of the brachioradialis The nerve was not disturbed Contraction to clinical examination did not appear in the brachioradialis until 40 weeks after the injury, that is, 14 weeks after it was obtained by direct and strong electrical stimulation of the nerve at operation

A possible explanation of this phenomenon is that functionally immature fibers were stimulated and that the ability to contract voluntarily depends on the presence of functionally mature fibers In this study it was the growth of the latter that was under investigation, and since it is impossible to evaluate the aforementioned phenomenon, which is probably operating in all muscles, though not necessarily to the same degree, its influence on the onset of recovery as detected by clinical examination has, perforce, been disregarded

In order to detect the earliest signs of recovery, patients were examined at weekly intervals until all muscles were contracting, from which time onward the examinations were conducted at monthly, then at three monthly and, finally, at six monthly intervals When weekly examinations were not possible and the first appearance of recovery could not therefore be limited accurately to a specific week, the last date when the muscle was known to be still paralyzed and the date when recovery was first detected were given in the tables

*Treatment*—Treatment in all cases consisted of daily massage, heat therapy, exercises and supervised and controlled splinting. Electrotherapy was not employed.

All muscles were splinted in a relaxed condition until contraction appeared. This point is mentioned specifically, because it is my experience that the onset of recovery may be delayed in unsupported muscles, whereas there is evidence to suggest that electrotherapy hastens the return of function. Consequently, since it would appear that the form of treatment affects to a certain extent the onset and progress of recovery, it is considered advisable to specify the treatment employed in any study of rates of regeneration.

#### END RESULTS

A brief resume of the end results is necessary for an appreciation of the clinical basis of this investigation. They have been summarized in table 1.

TABLE 1—*End Results in Sixty-Two Cases of Lesions of the Radial Nerve\**

Causative Injury	Spontaneous Regeneration	Combination of Spontaneous Re- generation and Tendon Transplant	Exploration			
			Irreparable Damage	Suture	Suture Under Tension	No Surgical Treatment Indicated
Simple compression	8					
Tourniquet	2					
Simple fracture of humerus	4					1
Laceration or penetrating in- jury	1		1	3		
Gunshot wound	12			1	1	
Gunshot wound and fracture of humerus	16	2	7	1	1	1
Total	43	2	8	5	2	2

\* The records are incomplete for 1 additional case.

In general patients with peripheral nerve injuries sustained in the Middle East campaigns were repatriated to Australia as soon as possible. Such patients were retained in the Middle East until suitable transport was available, and this delay, together with the time taken on the voyage home, lengthened considerably the interval between the date of the injury and the time when the patient came under observation in a base hospital in Australia. The late onset of spontaneous regeneration in a large proportion of these patients encouraged a conservative attitude in the treatment of those patients in whom the state of the nerve was not known.

Spontaneous regeneration proceeded either to completion or to a degree which contraindicated exploration of the nerve in 45 of the 62 cases investigated—in 1 other case the patient was transferred to another state before the onset of recovery. Of the 17 cases in which exploration was made, the nerve was irreparably damaged in 8, and in 2 cases it was sutured under tension. There was no recovery in these 2 cases,

forty-three and fifty weeks, respectively, after the suture. In 5 cases the nerves were sutured under favorable conditions, and of these, recovery was satisfactory in 4 and was proceeding satisfactorily in the fifth at the time of writing. In the remaining 2 cases the nerve was left undisturbed. In 1 of these 2 cases exploration of the nerve had been undertaken because of a statement in the field notes that it had been severed, but when exposed the nerve appeared normal. In the second (case 65, described later) interruption of conduction was still complete six months after the injury, at which time it was considered that spontaneous regeneration should have made its appearance if it were going to do so. The condition of the nerve is described in the section devoted to the pathologic study. Spontaneous regeneration appeared thirteen to forty weeks after neurolysis and proceeded to a satisfactory conclusion.

The observations may be summarized as follows:

- 1 The majority of lesions of the radial nerve recovered spontaneously and did not require exploration. This is in accord with the experience of others and accounts for the beneficial results often incorrectly attributed to neurolysis when this has been performed prematurely.

- 2 Conditions were favorable for suture in less than one-half the cases in which the condition of the nerve was not known but in which exploration was ultimately indicated.

- 3 The majority of the irreparable lesions were due to gunshot injuries accompanied by fracture of the humerus.

#### COURSE OF SPONTANEOUS REGENERATION AND REGENERATION FOLLOWING SUTURE

Provided regeneration commences simultaneously and advances at a uniform rate in all the axons and that after their entry into each muscle, the time taken for the nerve fibers to reestablish functional relationships is approximately the same, it may reasonably be expected that the various muscles should commence to contract in an order which is determined by the length of the fibers composing their motor branches from the site of injury to the muscle. The order of motor recovery is usually, but not necessarily, that in which the motor branches leave the nerve, since the first branch to a muscle may not be the shortest route to it.

The actual lengths of the motor fibers to the particular muscle they innervate, as measured along the nerve and its branches from a fixed point, were determined by dissection. According to these measurements, the test muscles are customarily innervated in the order of the

brachioradialis, the extensor carpi radialis longus, the extensor digitorum communis and extensor carpi ulnaris, the abductor pollicis longus and, finally, the extensor pollicis longus. In general the muscles were found to recover in this order. Departures from this serial reinnervation took one of three forms

1 Contraction in two neighboring muscles appeared simultaneously. This could be attributed either to the fact that the distances to be covered by the regenerating axons in each case were equivalent or approximately so or to the fact that the difference between those distances was so small that the onset of recovery must have occurred in both muscles within the time interval between examinations.

2 Contraction appeared almost simultaneously over the entire pattern. This usually occurred shortly after the injury was sustained and could be explained only on the basis that the distal segment had not undergone wallerian degeneration and that after a period of quiescence the entire pattern reawakened to activity. This form of recovery is characteristic of simple compression injuries.

3 There was a variation in the order of recovery of the muscle. Four factors may be responsible for this variation, and these may operate singly or in combination.

(a) The axons to the muscle taking abnormal precedence in the order of recovery may have a shorter distance to travel than those to muscles customarily recovering before it. The possible variations in the order of innervation of individual muscles (estimated on the basis of the shortest distances to each muscle from a fixed point on the radial nerve) have been reported separately. It is not uncommon, for example, for the extensor carpi ulnaris to be innervated before the extensor digitorum communis—in this series the former recovered before the latter in 5 of the 31 cases. Though Stopford<sup>2</sup> also recorded this variation, Seddon, Medawar and Smith<sup>3</sup> did not observe it and erroneously concluded that on anatomic grounds it could not occur.

(b) Axons for more proximally innervated muscles may be delayed at the site of injury for a period longer than those destined for more distally supplied muscles. The difference in the onset of regeneration at the site of injury must be sufficiently great to enable the latter to be reinnervated before the former.

(c) The site of injury may be such that the first, or higher, branches to a muscle, on which its early recovery depends, are directly involved, either severely or irreparably. Reinnervation of this muscle is then dependent on more distal branches, when such are present, and this involves a longer route to the muscle. By the time regenerating axons have covered this longer route muscles supplied by shorter

branches arising at higher levels are contracting. This, it is believed, accounts for the unusual delay occasionally seen in the reinnervation of the brachioradialis after wounds involving the nerve in the furrow.<sup>4</sup>

(d) All axons may not be involved to the same degree. This was well illustrated in case 114, in which the nerve was injured 24 cm. above the level of the lateral epicondyle. The extensor carpi radialis longus was observed to contract nine weeks and the brachioradialis sixteen weeks after the injury. The recovery of the extensor carpi radialis longus nine weeks after the injury could not be explained on the basis of complete wallerian degeneration occurring in the fibers to that muscle with a subsequent axonal growth distally unless this occurred at a rate far greater than that revealed by any investigation. Furthermore, although in 3 of 20 specimens examined anatomically the fibers to the extensor carpi radialis longus and the brachioradialis muscle were approximately equal in length, in no case were the fibers to the former shorter than those to the latter.

The only adequate explanation for the early recovery of the extensor carpi radialis longus is that the fibers supplying it had suffered an injury of the type defined by Seddon<sup>5</sup> as neurapraxia. In the case of the brachioradialis and the remaining muscles the onset of recovery was consistent with regeneration having followed complete wallerian degeneration after a short initial delay at the site of the injury.

#### PATHOLOGIC STUDY

*Observed Pathologic State*—Details relating to the wounds and the nature of the nerve injuries are to be provided in another paper. Only a brief account is necessary for the purposes of the present discussion.

In the following 3 cases the nerve was sutured, and the times of recovery for the individual muscles (table 2) date from the time of suture.

CASE 40—There was complete severance of the nerve in the furrow, due to a gunshot injury. Secondary suture was done forty-four weeks later.

CASE 180—There was complete severance of the nerve in the furrow, due to a bayonet injury. The nerve was sutured thirty-eight days later.

CASE 282—There was almost complete severance of the nerve in the spiral groove due to injury from an ax. Primary suture was done.

In the remaining cases complete interruption of conduction was followed by spontaneous regeneration. In 22 cases the nerve was not seen. In the rest the

4 "Furrow" indicates the intermuscular furrow outlined between the brachialis muscle, medially, and the brachioradialis and extensor carpi radialis longus muscles, laterally.

5 Seddon, H. J. A Classification of Nerve Injuries, *Brit. M. J.* 2: 237-239, 1942; Three Types of Nerve Injury, *Brain* 66: 238-288, 1943.



condition of the nerve was reported in the battle notes or at subsequent exploration, as follows

CASE 65—Simple comminuted fracture of the upper third of the shaft of the right humerus was present. The radial nerve was explored from the axilla to the spiral groove twenty-four weeks after the injury. It was adherent to the humerus at the site of fracture and was freed with difficulty. A small neuroma was situated just above the point where the nerve was firmly adherent to bone,

TABLE 2—*Time and Order of Motor Recovery in Thirty-One Cases of Complete Interruption of Conduction of Radial Nerve*

Case No	Causative Injury	Level of Injury Above Epicondyle, Cm	Infection *	Scarring *	Return of Voluntary Contraction,† Weeks									
					BR	ECRL	EDC	ECU	APL	EPL				
65	Simple fracture	24.0	Nil	Nil	37.64	37.64	37.64	37.64	37.64	37.64				
77	Simple fracture	10.0	Nil	Nil	16	18	23	23	25	27				
161	Simple fracture	10.0	Nil	Nil	13	14	21	23	25	28				
232	Simple fracture	10.0	Nil	Nil	9	8.5	8.5	8.5	9	9				
317	Simple fracture	10.0	Nil	Nil	16	18	24	22	25	29				
195	Laceration	15.0	Nil	Nil	11.14	11.14	18	19.23	19.23	19.23				
114	Gunshot wound	24.0	I	Nil	16	9	19	19	27	28				
185	Gunshot wound	12.0	Nil	Nil	14	16	22	24	26	30				
244	Gunshot wound	15.0	Nil	S	6	6	28	28	29.46	29.46				
27	Gunshot wound	12.5	Nil	Nil	Intact‡	3	13	19	13	21				
64	Gunshot wound	11.0	Nil	Nil	22.29	22	22.29	22.29	22.29	22.29				
79	Gunshot wound	10.0	Nil	Nil	4-18	4.18	21	26	28.30	28.30				
203	Gunshot wound	9.0	Nil	Nil	20	20	27	27	31	31				
255	Gunshot wound	2.0	I	S	8	8	18	18	20	26				
264	Gunshot wound	1.0	Nil	S	Intact	14	23	23	25	34				
69	Gunshot wound	Furrow	I	S	Intact	14.20	13	14.20	14.20	25				
97	Gunshot wound	Furrow	I	S	Intact	12	22	17	22.58	22.58				
202	Gunshot wound	Furrow	I	S	14	14	8	14	10	10				
99	Gunshot wound + fracture	20.0	I	S	26.28	24	26.28	26.28	26.28	33				
18	Gunshot wound + fracture	19.0	I	S	51.76	28.30	23.30	23.30	23.30	23.30				
214	Gunshot wound + fracture	15.0	I	S	3	3	5	5	6	6				
231	Gunshot wound + fracture	12.5	I	S	40	42	50	45	50	56				
234	Gunshot wound + fracture	12.5	Nil	Nil	6	6	10.14	10.14	10.14	10.14				
72	Gunshot wound + fracture	11.0	Nil	Nil	Intact‡	20	20.30	20.30	20.30	20.30				
118	Gunshot wound + fracture	9.0	I	S	16	17.20	17.20	17.20	28	28				
100	Gunshot wound + fracture	7.5	I	S	Intact	23	28.31	28.31	32.36	32.36				
106	Gunshot wound + fracture	5.0	I	S	17	20	27	30	31	36				
258	Gunshot wound + fracture	5.0	I	S	18	22	32	31	35	37				
	Suture													
282	Laceration	12.5	Nil	Nil	22	27	37	36	40	45				
180	Laceration	4.0	Nil	S	28	20	31	31	34	42				
40	Gunshot wound	5.0	I	S	Intact	20	34	35	40	40				

\* I and S indicate significant infection and scarring, respectively

† In this table, BR indicates brachioradialis, ECRL, extensor carpi radialis longus; EDC, extensor digitorum communis; ECU, extensor carpi ulnaris; APL, abductor pollicis longus; and EPL, extensor pollicis longus

‡ The muscle was originally paralyzed but was contracting when I first examined it

and a second neuroma was observed 2.5 cm above this. Between the neuromas the nerve was much thinned out. Stimulation of the nerve immediately above and below the neuromas produced no response. Excision of the involved segment was demanded, but this would have necessitated the insertion of a graft, and, in the anticipation that the neurolysis might encourage regeneration, further repair

work on the nerve was abandoned. Spontaneous regeneration appeared 13 to 40 weeks later and proceeded to a satisfactory conclusion.

CASE 202—The nerve was observed in the furrow and appeared normal.

CASE 203—There were contusion and superficial laceration of the nerve in the furrow.

CASE 231—It was reported that the nerve was torn and a piece blown away. On the basis of this information, and since no contraction could be detected clinically, the nerve was explored twenty-six weeks after the injury. It was observed to be in continuity and appeared normal, and stimulation above the level of injury resulted in feeble contraction of the brachioradialis. The original report was obviously incorrect.

CASE 244—The nerve was traumatized and hemorrhagic in the spiral groove but was not severed.

CASE 264—The nerve was reported to be completely severed in the furrow. No repair was effected. The lesion appeared to be complete clinically. The subsequent progress of recovery, which terminated in complete restoration of function, suggested that the severed nerve seen was not the radial nerve.

*Deduced Pathologic State*—An assessment of the nature of the nerve injury was attempted on the basis of the course of regeneration. In cases 18, 64, 65, 72, 79, 97, 100 and 195 there were insufficient data available to permit this.

The course of motor regeneration in cases 214, 232 and 234 closely resembled that following simple compression injuries of the radial nerve. In these 3 cases and in the group of cases of simple compression injury muscles innervated at different distances from the site of injury burst into activity simultaneously. The accumulated evidence, both clinical and experimental, supports the belief that the histopathologic changes leading to interruption of conduction in simple compression injuries must differ in some respects at least from the changes seen after a breach of continuity of the nerve fibers. These changes are reversible and apparently do not involve wallerian degeneration.

The observations in the 3 cases mentioned, however, differed from those in cases of simple compression injuries in certain important particulars.

(a) The length of the quiescent period was greater than that observed in any of the cases of simple compression injury. The present observations suggest that nerves may cease to conduct for 63 days and yet reawaken to activity without invoking any of the changes associated with wallerian degeneration and the regenerative process which follows it.

(b) In all 3 cases the superficial radial nerve was involved (in case 234 the dorsal cutaneous nerve of the forearm was independently divided). Sensation in the field of the superficial radial nerve was still defective sixty, seventy-three and forty-five weeks after the lesions,

which was long after motor recovery was complete. The occurrence and persistence of sensory defects are in contrast to the condition obtaining in cases of simple compression injuries, in which sensation is usually undisturbed. As has been pointed out, however (Sunderland<sup>1</sup>), sensory defects do appear with the more severe simple compression injuries, and when they are well established restoration of full motor function is considerably delayed. The present observations confirm this.

(c) Wasting persisted longer than with injuries due to simple compression. Estimation of wasting which could be definitely attributed to the lesion of the radial nerve was not possible in cases 232 and 234, owing to the presence of an associated lesion of the median nerve. In case 214 wasting, which could be attributed to the lesion of the nerve, was still present to the extent of 11 cm above and 2 cm below the lateral epicondyle sixty weeks after the injury. Wasting was observed in the cases of simple compression injury, but in no case did it persist for this length of time.

(d) Recovery of motor power was slow. In cases 232 and 234 there was an associated lesion of the median nerve. So far as could be ascertained in the presence of this complication, motor power was restored to normal thirty-one (case 232) and thirty-two (case 234) weeks after the injury. In case 214 the average dynamometric readings for the grip sixty weeks after the injury were 270 and 330 millimeters for the right and left hands, respectively (the patient was right handed). The slow recovery of power was a feature of these cases. On the other hand, rapid restoration to full power was a feature of the cases of simple compression injury.

These 3 cases present features which are implied in the terms "neurapraxia" and "axonotmesis," as defined by their originators.

The persistence of weakness, wasting and sensory defects for considerable periods after the injury indicated an intraneural disturbance of sufficient severity to result in peripheral degeneration followed by delayed or incomplete regeneration of all the fibers destined for each motor and sensory unit. The course of the regeneration indicated that there had been little, if any, disturbance of the intraneural fascicular pattern, though the persistence of residual sequelae may be evidence that this had occurred in some small measure. All these features are characteristic of the type of injury referred to by Seddon<sup>5</sup> as axonotmesis.

On the other hand, evidence of a neurapraxic state was reflected in the recovery of muscles which occurred either simultaneously or within sufficiently brief intervals to exclude recovery on the basis of axons advancing distally over different fiber-lengths, and in the rapidity of recovery in individual muscles which were innervated at such distances from the lesion that this recovery could not possibly

have been due to the growth of axons at anything approaching the estimated rates. However, the considerable delay (up to sixty-three days) in the onset of motor recovery in cases which otherwise conform to this type is an unusual feature, and if they are to be included in the neurapraxic group the definition of the latter should be extended to include delayed motor recovery.

It would thus appear that in cases 214, 232 and 234 there was a mixed lesion, in which the greater proportion of the total number of fibers to every muscle suffered a prolonged axoplasmic disturbance not leading to peripheral degeneration, while the remainder suffered a sufficiently severe injury to lead to wallerian degeneration.

A study of the rate and order of motor regeneration in conjunction with the level of the lesion in cases 27, 114, 202 and 244 indicated that the injury was not uniform throughout the nerve. The early recovery of certain muscles and the order of that recovery could be explained only on the basis of delayed concussion or neurapraxia, while the course of regeneration pursued by the others was in conformity with the intrafascicular interruption of fibers, which has been termed axonotmesis.

The time and order of recovery of the muscles in cases 69 and 99 suggested that wallerian degeneration had preceded regeneration but that the fibers and tissues at the site of injury were not uniformly involved, as a result of which some fibers preceded others in the regenerative process.

The manner in which recovery appeared, the rate and order in which it proceeded and the end result in cases 77, 106, 118, 161, 185, 203, 231, 255, 258, 264 and 317 were proof of a lesion of the type defined as axonotmesis. Though the lesions were not of equivalent severity in these cases (see later section), the evidence indicated that all the fibers and tissues at the site of injury were in each individual case damaged to approximately the same degree, the changes involving peripheral degeneration, with the subsequent spontaneous reinnervation of the distal segment.

A comparison of the observed and the deduced pathologic condition of the nerve and the onset of recovery in each muscle in cases 202, 203 and 244 suggests that the appearance of the nerve at the time of injury is a fairly reliable guide to the probable duration of the entire regenerative process, though it is not necessarily an accurate guide to the condition of individual fibers, since neurapraxia may occur with what appear to be severe injuries and axonotmesis in nerves which seem to be normal.

#### RATE OF REGENERATION

*Method*—The methods at present available for estimating rates of regeneration in peripheral nerves in man following injury have recently been summarized by Seddon, Medawar and Smith.<sup>3</sup>

In the present investigation an additional method has been employed for calculating the rate of regeneration of motor axons. It is based on the time interval between the injury and the onset of recovery in two muscles and the shortest distance to each of them from the site of injury.

The equation for estimating the rate of regeneration is derived in the following manner (figure)

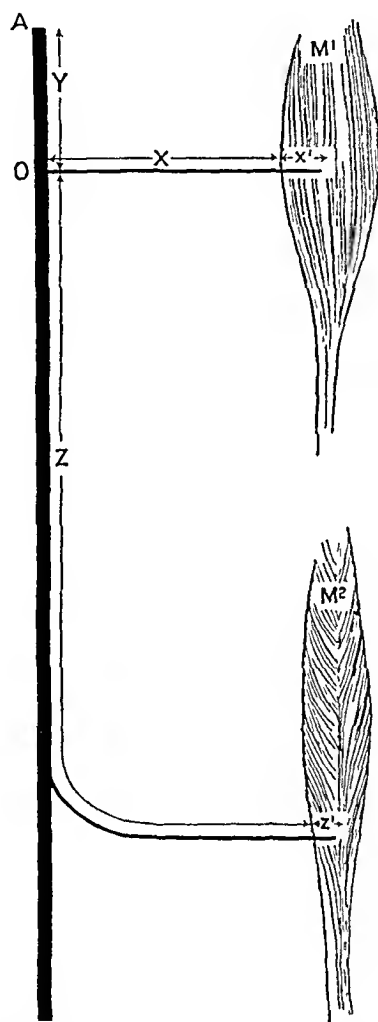


Diagram showing factors in derivation of equation for estimating rate of regeneration of the radial nerve

$A$  is a point on the nerve proximal to the site of origin of its branches

$y + x$  equals  $L_1$ , the shortest distance to  $M_1$ , the more proximally supplied of two muscles, from the point  $A$

$y + z$  equals  $L_2$ , the shortest distance to  $M_2$ , the more distally supplied of two muscles, from the point  $A$

$x_1$  and  $z_1$  are the intramuscular distances in  $M_1$  and  $M_2$  respectively, which must be covered by regenerating axons before voluntary contraction is possible

$T^1$  and  $T^2$  represent the times elapsing, in days, between the injury and the appearance of contraction in  $M^1$  and  $M^2$  respectively

$d$  and  $D$  represent the initial delays elapsing before regeneration commences in axons destined for  $M^1$  and  $M^2$  respectively

$t^1$  and  $t^2$  are the times elapsing subsequent to the entry of axons into  $M^1$  and  $M^2$  respectively, and before functional neuromuscular relations are reestablished and voluntary contraction is possible

The regenerating axons, therefore, travel  $(y + v + v^1)$  mm in  $T^1 - (d + t^1)$  days and  $(y + s + s^1)$  mm in  $T^2 - (D + t^2)$  days

Assuming that

(a) The delay at  $A$ , the site of injury or suture, is the same for regenerating axons destined for  $M^1$  and  $M^2$

(b) The time taken by regenerating axons to travel the same distance in nerve fibers for different muscles is the same

(c) The distance which must be covered intramuscularly ( $v^1$  and  $s^1$ ) and the time ( $t^1$  and  $t^2$ ) elapsing in each instance before functional neuromuscular relations are reestablished and voluntary contraction is possible are identical

it may be inferred that

The time taken to travel  $(y + s) - (y + v)$  mm is  $T^2 - T^1$  days

Since  $(y + s)$  and  $(y + v)$  are the shortest routes to  $M^2$  and  $M^1$ , respectively

$$\text{The rate, } R, \text{ in millimeters per day} = \frac{L^2 - L^1}{T^2 - T^1}$$

Values for the lengths  $L^1$  and  $L^2$  were obtained for a series of muscles from an anatomic investigation of the radial, median, ulnar and sciatic nerves in 20 specimens. These will be reported separately. The lengths were measured directly along the nerve and its branches between a fixed point on the former and the site of entry of the branch into the muscle and in the case of multiple branches over the shortest route to the muscle. The exact position of the fixed point is, however, immaterial, since the distance along the nerve from it to the origin of the branch destined for the more proximally innervated muscle is common to the measurement for both the proximal and the distal muscles.

Values for the times,  $T^1$  and  $T^2$ , calculated in days from the time of injury to the onset of recovery in the muscles were obtained from clinical studies of selected cases of peripheral nerve injuries in which the following conditions obtained

1 Interruption of conduction was complete and associated with wallerian degeneration

2 The onset and progress of recovery were such as to indicate uniform involvement of the fibers at the site of injury

3 The onset and progress of recovery were such as to support the hypothesis that the axons commenced to regenerate at approximately the same time

4 Any departure from the normal order of recovery could be satisfactorily explained on the basis of established anatomic variations

In this way, factors which would invalidate the assumptions on which the equation depends were reduced to a minimum or were entirely eliminated

It should be emphasized that this method is concerned only with the rate of growth of functionally mature fibers, since it depends on estimates of the progressive reestablishment of function. In common with all others, it neglects the distance

TABLE 3—Measurements of Rates of Regeneration of Radial Nerve

A Values for  $L^2 - L^1$ 

Specimen	Distances, Millimeters *									
	BR E O R L	BR E D C	BR E C U	E C R L F D C	E C R L F C U	E D C A P L	F O U A P L	I D C E P L	E C U E P L	A P L E P L
1	1	114	91	113	90	5	23		8	
2	11	111	114	100	103	10	7	29	26	19
3		108	93	111	96	11	26	23	38	12
4	23	128	118	105	95	5	15	72	82	67
5	19	124	135	105	116	24	13	39	28	15
6	48	147	149	99	101	12	10	37	35	25
7	5	96	103	91	98	16	9	54	47	38
8	9	92	91	83	82	18	19	33	34	15
9	50	166	166	116	116			9	9	9
10	25	142	126	117	101		16	29	45	29
11	15	136	132	121	117			35	39	55
12	24	107	114	83	90	33	26	49	42	16
13	28	133	116	105	88		11	16	33	22
14	30	114	124	84	94	65†	55†	30	20	
15	16	125	125	109	109	4	4	40	40	36
16	21	120	136	99	115			56	40	63
17	45	95	93	50	53	6	3	58	55	52
18	25	97	104	72	79	32	25	57	50	25
19	30	139	150	109	120	10		40	29	30
20	40	113	119	73	79	25	19	40	34	15
Mean of differences	25	120	120	93	97	15	15	39	37	30
Standard deviation	14	20	21	10	17	10	8	16	16	18

B Values for  $T^2 - T^1$ 

## Times Weeks

Nature of Injury	BR E O R L	BR E D C	BR E C U	E C R L F D C	E C R L F C U	E D C A P L	F O U A P L	I D C E P L	E C U E P L	A P L E P L
Axonotmesis										
Case 77	2	7	7	5	5	2	2	4	4	2
Case 106	3	10	13	7	10	4	1	9	6	5
Case 161	1	8	10	7	9	4	2	7	5	3
Case 185	2	8	10	8	8	4	2	8	6	4
Case 203		7	7	7	7	4	4	4	4	
Case 231	2	10	5	8	3		5	6	11	6
Case 255		10	10	10	10	2	2	8	8	6
Case 258	4	14	13	10	9	3	4	5	6	2
Case 264				9	9	2	2	11	11	9
Case 317	2	8	6	6	4	1	3	5	7	4
Mean of differences	2.3	9.1	9.0	7.5	7.4	2.9	2.7	6.7	6.8	4.6
Suture										
Case 40				14	15	6	5	6	5	
Case 180				11	11	3	3	11	11	8
Case 282	5	15	14	10	9	3	4	8	9	5
Mean of differences				11.7	11.7	4.0	4.0	8.3	8.3	6.5

TABLE 3—Measurements of Rates of Regeneration of Radial Nerve—Continued

C Rates of Regeneration, in Millimeters per Day						
Nerve Segment Over Which Rate Was Estimated	Anastomosis					Suture (3 Cases Only)
	Distance, L, in Mm	Time, T, in Weeks	Mean Rate from Mean L and T	Rate from L+ and T+	Rate from L- and T-	
BR to ECRL	25 ± 14	23 ± 0.9	1.6	1.7	1.1	
BR to EDC	120 ± 20	91 ± 2.2	1.9	1.8	2.1	
BR to ECU	120 ± 21	90 ± 2.9	1.9	1.7	2.3	
ECRL to LDC	98 ± 19	75 ± 1.7	1.9	1.8	1.9	1.2
ECRL to ECU	97 ± 17	74 ± 2.5	1.9	1.6	2.3	1.2
EDC to APL	15 ± 10	2.9 ± 1.2	0.7	0.9	0.4	0.5
ECU to APL	15 ± 8	2.7 ± 1.2	0.8	0.8	0.7	0.5
EDC to EPL	39 ± 16	6.7 ± 2.3	0.8	0.9	0.7	0.7
ECU to EPL	37 ± 16	6.8 ± 2.5	0.8	0.8	0.7	0.6
APL to EPL	30 ± 18	4.6 ± 2.2	0.9	1.0	0.7	0.7

\* In this table, BR indicates brachioradialis, ECR L, extensor carpi radialis longus, EDC, extensor digitorum communis, ECU, extensor carpi ulnaris, APL, abductor pollicis longus, and EPL, extensor pollicis longus.

† Value discarded

which must be covered intramuscularly by the regenerating axons before voluntary contraction is possible and the time elapsing between the entry of axons into the muscle and the appearance of voluntary contraction. However, these factors are constantly present in all muscles, and, though they are not necessarily equivalent, it is reasonable to assume that if any dissimilarity does exist it is so small as to be unimportant.

Since it cannot be assumed that the rate is constant over the entire length of the nerve, this method should not be employed for calculating rates between the first and the last muscle innervated by the nerve when a considerable distance separates them. The rates should be independently calculated for proximal and distal segments of the nerve, and muscles should be so selected that the distances between them are such that any diminution in rate which would occur over them, and which would thereby invalidate the equation, is reduced to insignificant proportions or is entirely eliminated. In this investigation, the rate was calculated separately over the proximal (brachioradialis to extensor carpi radialis longus, brachioradialis and extensor carpi radialis longus to extensor digitorum communis and extensor carpi ulnaris, respectively), intermediate (extensor digitorum communis and extensor carpi ulnaris to abductor pollicis longus) and distal (extensor digitorum communis, extensor carpi ulnaris and abductor pollicis longus to extensor pollicis longus) portions of the radial nerve. No attempt was made to calculate the rate of regeneration over extensive lengths, as would be the case if, for example, the brachioradialis and the extensor pollicis longus were used as the test muscles.

Advantages of the method here described are that it renders unnecessary a knowledge of the level of the injury and the delay occurring at that site before the commencement of regeneration. Furthermore, the rate of regeneration can be estimated separately over different segments of the nerve by selecting muscles which are innervated at different levels, a condition which, in turn, means that it is then possible to ascertain whether regeneration proceeds uniformly during the entire process or whether its rate diminishes progressively. It is not possible, however, to estimate by this means the rate over that section of the nerve which is proximal to the origin of its first branch, since the portion of the nerve pattern over which the rate is estimated actually commences at a point on the



main trunk which is distal to the origin of the branch to  $M^1$  by the length of that branch

The rate of regeneration can be estimated in any individual case, or an average rate, calculated from mean readings for  $T^1$  and  $T^2$ , can be obtained from observations in a large series of cases. With the former method the considerable and unpredictable range of variations in the length of the shortest fibers to the same muscle in different persons must be taken into consideration. This factor was not mentioned, and was apparently disregarded, by Seddon, Medawar and Smith<sup>3</sup> when calculating, by another method, their rates of regeneration. When the rate is calculated on mean readings for  $L$  and  $T$  in a large number of cases, as has been done in this study, it is believed that this unpredictable element is reduced to a minimum. By averaging the lengths and times ( $L$  and  $T$ ) for any group of muscles, those factors peculiar to an individual case which may influence the rate of regeneration are disregarded. However, it is an average estimate of the rate of regeneration which is being sought, since, regardless of the method employed, the rate peculiar to any individual case can be calculated only in retrospect—that is, after regeneration has advanced over suitable lengths of the nerve.

Values for  $L^2 - L^1$  for the radial nerve are given in table 3 A. All measurements were made along the nerve and its branches from a point 10 cm above the lateral epicondyle.

Values for  $T^2 - T^1$  are given in table 3 B. Only cases 77, 106, 161, 185, 203, 231, 255, 258, 264 and 317 fulfilled the required conditions, while cases 40, 140 and 180 proved suitable for a study of rates of regeneration following nerve suture. In the few instances in this series in which two to three weeks separated examinations muscles showing recovery at the second examination were considered to have recovered midway between the two.

The mean rates of regeneration, calculated in millimeters per day between brachioradialis and extensor carpi radialis longus, brachioradialis and extensor digitorum communis, brachioradialis and extensor carpi ulnaris, extensor carpi radialis longus and extensor digitorum communis, extensor carpi radialis longus and extensor carpi ulnaris, extensor digitorum communis and abductor pollicis longus, extensor carpi ulnaris and abductor pollicis longus, extensor digitorum communis and extensor pollicis longus, extensor carpi ulnaris and extensor pollicis longus, and abductor pollicis longus and extensor pollicis longus are given in table 3 C.

No attempt has been made to estimate, by the method here described, the standard deviations of the rates of regeneration over those portions of the nerve pattern investigated. However, in studying the possible influence of the standard deviations of the lengths and of the times, which have been recorded, on the rates of regeneration, it seems reasonable to assume that in the regenerative process high and low values for the times would most probably correspond to high and low values, respectively, for the lengths. Calculations have been made on this basis, and the estimated rates for the high and low values of the lengths and times, respectively, have been included with the mean rates in table 3 C.

*Results*—Except for a pronounced discrepancy in the rates calculated over the portions of the nerve pattern from extensor digitorum communis and extensor carpi ulnaris to abductor pollicis longus, there was little variation in the three rates calculated for each and corresponding portions of the nerve. A possible explanation of this discrepancy is the unusually high value obtaining for the lengths extensor digitorum communis and extensor carpi ulnaris, respectively, to abductor

pollicis longus in 1 specimen (case 14), since when this specimen was discarded for the purposes of estimating the rate of regeneration over these two portions of the nerve (as was done in calculating the rates recorded in table 3 C) the three calculated rates then approximated

*Comment*—From these results it is suggested that the mean rate over the proximal portions of the pattern is greater than that over the distal portions and that the difference in the mean rates is sufficiently great to indicate that there is a progressive diminution in rate as regeneration advances. It would appear, however, that in the initial stages the rate diminishes rapidly over the proximal portions of the nerve and then, fifty to one hundred days after the first appearance of recovery, becomes relatively constant at 0.8 mm per day over the distal portions.

Though it is not justifiable to draw dogmatic conclusions on the basis of 3 cases, the evidence would suggest that the rate of regeneration following suture is, in the initial stages at least, less than that following axonotmesis but that later, one hundred to one hundred and fifty days after the first appearance of recovery, the rate approximates that following axonotmesis.

Seddon, Medawar and Smith<sup>3</sup> inferred from their calculations that "the rate of regeneration is initially as high as 3 mm a day, and that it falls off progressively down to and then below a value of the order of 1 mm a day about 100 days after recovery has started." However, they concluded that the rate could be regarded as "constant over the moderate ranges of time and distance over which the process was recorded in the great majority of the cases described." With their method for estimating rates of regeneration, they recorded rates of  $1.6 \pm 0.2$  mm per day following suture and of  $1.5 \pm 0.1$  mm per day in cases of axonotmesis. These values are in certain respects at variance with the results in this investigation. On the basis of data obtained from Stopford's records, these authors calculated that the rate of regeneration following suture was  $0.56 \pm 0.03$  mm per day, which approximates the rate calculated over the distal portions of the sutured nerves in the present study.

There was no significant relationship between the age of the patient (in this series the ages varied from 19 to 30 years) and the course of regeneration, and therefore it was not possible to determine whether or not regeneration proceeds at a faster rate in young persons.

#### LATENT PERIOD INTERVENING BETWEEN TIME OF INJURY AND ONSET OF RECOVERY

The following information has been correlated in table 4: (a) the agent responsible for the injury, (b) the level of the injury with reference to the lateral epicondyle, (c) the degree of infection and scarring,

though the wound was not infected, the residual scarring was considerable. In case 40 there was a considerable degree of infection of the wound in the initial stages and scarring, while secondary suture was not performed until eleven months after the injury. However, considering the complications operating in cases 40 and 180, the difference in the periods of delay is remarkably small. A possible explanation of this is that a well executed suture, in the absence of infection, converts the lesions in all cases into injuries of equivalent severity. The data in case 40 also indicate that a delay of eleven months before suture did not materially influence either the initial delay or the course of regeneration.

*Comment*—From the data available, it would appear that the duration of the initial delay is a measure of the severity of the nerve injury. In establishing this relationship, the observations in the simple fracture and suture groups were of particular significance.

In the simple fracture group infection and scarring were absent, and the roentgenographic and clinical data indicated that the nerve had been damaged at a corresponding level in all 3 cases. From the nature of the causative injury and the order and rate of regeneration which corresponded closely in all 3 cases, it appeared that the extent of the injury was similar and of minimal degree in each case. The initial delay was approximately 10, 10 and 7 weeks, respectively.

The course of regeneration in case 118, of the gunshot wound group, in which there were significant infection and scarring, closely resembled that observed in the simple fracture group. It seems reasonable to assume, therefore, that the extent of the injury in this case was similar and that infection and local scarring had provided no obstacle to regeneration.

Though the causative injury, the condition of the wound and the interval between the injury and the time of suture varied widely in the cases comprising the suture group, the course of regeneration corresponded fairly closely in the 3 cases. Here, disregarding the influence of infection and local scarring, the injury was known to be maximal in extent and the initial delays observed were 14, 15.9 and 16.6 weeks, respectively. The calculated initial delays in cases 100, 106, 203 and 258 approximated those in the suture group. Presumably, in these cases the injury was of greater severity than that observed in the simple fracture group.

Between these two groups will be found all intervening grades of severity of injury, which will account for intermediate variations in the initial delays. Thus, in cases of axonotmesis the severer the injury the closer will the course of regeneration approximate the sequence of events following suture.

The observed initial delay in case 231 was 32 weeks. This was the extreme maximum delay observed and was not approached in any other case. Its presence, however, is sufficient to indicate that delays beyond 17 weeks do occur.

Seddon, Medawar and Smith<sup>1</sup> claimed that "there is no doubt whatever that the latent period after suture is longer than that after axonotmesis." An examination of the initial delays recorded in table 4 provides evidence that this is not invariably the case.

#### INFLUENCE OF DURATION OF LATENT PERIOD ON SUBSEQUENT COURSE OF REGENERATION

The course of regeneration subsequent to the onset of recovery may be expressed in terms of the time taken to reinnervate the entire pattern as measured from the onset of recovery in the first and the last muscle to recover. This period varied from 11 to 23 weeks. It was minimal in the simple fracture group and maximal in the suture group.

There are four possible explanations of the observed differences in the time taken to reinnervate the pattern.

- 1 The linear extent of the pattern is known to vary over wide limits in different persons. The recorded differences are of such magnitude that these alone could account for the observed differences in time.

- 2 The rate of regeneration may vary in different persons. It is extremely unlikely that the rate is a constant one, though the possible range of variations is unknown. It is improbable, however, that this factor alone would account for the observed differences in the time taken to reinnervate the pattern.

- 3 Some nerve fibers may be more severely damaged than others, and this may introduce a variation in the initial delay for different fibers. That this may occur has been deduced from the sequence of events following the injury in cases 27, 69, 99, 114, 202 and 244, in which the order of recovery was so deranged that the cases were discarded for the purposes of this investigation. To explain the variations in the time taken to reinnervate the entire pattern on this basis, the onset of regeneration in the fibers destined for either the first or the last muscle to recover, or both, must be delayed, though not in such a way as to disturb the normal serial order of recovery.

- 4 It may be that the over-all rate of regeneration is slower in cases in which the initial delay is longer, that is, in cases in which the injury has been more severe but in which it has, nevertheless, been equally distributed over all the fibers at the level of the injury.

If the duration of the initial delay is any guide to the severity of the injury, and there is some evidence to indicate that it is, then it

main trunk which is distal to the origin of the branch to  $M^1$  by the length of that branch

The rate of regeneration can be estimated in any individual case, or an average rate, calculated from mean readings for  $T^1$  and  $T^2$ , can be obtained from observations in a large series of cases. With the former method the considerable and unpredictable range of variations in the length of the shortest fibers to the same muscle in different persons must be taken into consideration. This factor was not mentioned, and was apparently disregarded, by Seddon, Medawar and Smith<sup>3</sup> when calculating, by another method, their rates of regeneration. When the rate is calculated on mean readings for  $L$  and  $T$  in a large number of cases, as has been done in this study, it is believed that this unpredictable element is reduced to a minimum. By averaging the lengths and times ( $L$  and  $T$ ) for any group of muscles, those factors peculiar to an individual case which may influence the rate of regeneration are disregarded. However, it is an average estimate of the rate of regeneration which is being sought, since, regardless of the method employed, the rate peculiar to any individual case can be calculated only in retrospect—that is, after regeneration has advanced over suitable lengths of the nerve.

Values for  $L^2 - L^1$  for the radial nerve are given in table 3 A. All measurements were made along the nerve and its branches from a point 10 cm above the lateral epicondyle.

Values for  $T^2 - T^1$  are given in table 3 B. Only cases 77, 106, 161, 185, 203, 231, 255, 258, 264 and 317 fulfilled the required conditions, while cases 40, 140 and 180 proved suitable for a study of rates of regeneration following nerve suture. In the few instances in this series in which two to three weeks separated examinations muscles showing recovery at the second examination were considered to have recovered midway between the two.

The mean rates of regeneration, calculated in millimeters per day between brachioradialis and extensor carpi radialis longus, brachioradialis and extensor digitorum communis, brachioradialis and extensor carpi ulnaris, extensor carpi radialis longus and extensor digitorum communis, extensor carpi radialis longus and extensor carpi ulnaris, extensor digitorum communis and abductor pollicis longus, extensor carpi ulnaris and abductor pollicis longus, extensor digitorum communis and extensor pollicis longus, extensor carpi ulnaris and extensor pollicis longus, and abductor pollicis longus and extensor pollicis longus are given in table 3 C.

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**Results**—Except for a pronounced discrepancy in the rates calculated over the portions of the nerve pattern from extensor digitorum communis and extensor carpi ulnaris to abductor pollicis longus, there was little variation in the three rates calculated for each and corresponding portions of the nerve. A possible explanation of this discrepancy is the unusually high value obtaining for the lengths extensor digitorum communis and extensor carpi ulnaris, respectively to abductor

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Though it is not justifiable to draw dogmatic conclusions on the basis of 3 cases, the evidence would suggest that the rate of regeneration following suture is, in the initial stages at least, less than that following axonotmesis but that later, one hundred to one hundred and fifty days after the first appearance of recovery, the rate approximates that following axonotmesis.

Seddon, Medawar and Smith<sup>3</sup> inferred from their calculations that "the rate of regeneration is initially as high as 3 mm a day, and that it falls off progressively down to and then below a value of the order of 1 mm a day about 100 days after recovery has started." However, they concluded that the rate could be regarded as "constant over the moderate ranges of time and distance over which the process was recorded in the great majority of the cases described." With their method for estimating rates of regeneration, they recorded rates of  $1.6 \pm 0.2$  mm per day following suture and of  $1.5 \pm 0.1$  mm per day in cases of axonotmesis. These values are in certain respects at variance with the results in this investigation. On the basis of data obtained from Stopford's records, these authors calculated that the rate of regeneration following suture was  $0.56 \pm 0.3$  mm per day, which approximates the rate calculated over the distal portions of the sutured nerves in the present study.

There was no significant relationship between the age of the patient (in this series the ages varied from 19 to 30 years) and the course of regeneration, and therefore it was not possible to determine whether or not regeneration proceeds at a faster rate in young persons.

#### LATENT PERIOD INTERVENING BETWEEN TIME OF INJURY AND ONSET OF RECOVERY

The following information has been correlated in table 4: (a) the agent responsible for the injury, (b) the level of the injury with reference to the lateral epicondyle, (c) the degree of infection and scarring,

(*d*) the time taken for the first and the last muscle to recover, together with the interval between these periods, and (*e*) the calculated initial delay, in weeks, occurring at the site of injury

It is believed that in cases 77, 161 and 317 the nerve was damaged where it passed through the lateral intermuscular septum—anatomic studies have placed this point approximately 10 cm above the lateral epicondyle. The nerve was sutured in case 282 at the distal end of the spiral groove and in cases 180 and 40 immediately above and below the supply to the brachioradialis, respectively

The latent period preceding the onset of recovery comprises and is determined by (*a*) the initial delay, *t*, occurring at the site of injury and (*b*) the time, *t*<sup>1</sup>, taken by the regenerating axons to advance from that point to the first muscle recovering. The level of the injury will influence the second component but not necessarily the first. Allowing for

TABLE 4—*Shortest Distances (in Millimeters) to Muscles Supplied by the Radial Nerve\**

	Measurements Taken from Point 10 Cm Above Lateral Epicondyle †		Measurements Taken from Lateral Epicondyle †			
	BR	E C R L	E C U	E D C	A P L	E P L
Mean	82	105	102	102	114	139
Standard deviation	15	11	20	21	21	23

\* These measurements were employed in calculating the initial delay

† In this table, BR indicates brachioradialis, E C R L, extensor carpi radialis longus, E D C, extensor digitorum communis, E C U, extensor carpi ulnaris, A P L, abductor pollicis longus, and E P L, extensor pollicis longus

the differences in the level of the lesion, initial delays of short and long duration produce an early and a late onset of recovery, respectively

Component *t*<sup>1</sup> can be calculated from the distance from the site of injury to the first muscle contracting and the estimated rate of regeneration. The shortest distances to the muscles supplied by the radial nerve were measured in 20 specimens directly along the nerve and its branches between a fixed point on the former and the site of entry of the branch into the muscle. Measurements relevant to this paper are given in table 4, and from these the distance from the site of the injury to the first muscle contracting can be calculated provided the level of the injury is known with reference to the fixed point. Over the proximal sections of the nerve, between the brachioradialis and extensor carpi radialis longus, above, and the extensor digitorum communis, below, the rate has been found to be 1.9 mm per day. Since, however, the rate has been shown to diminish progressively as regeneration proceeds, it is conceivable, and extremely likely, that the growth may be more rapid at higher levels than at those for which the rate of 1.9 mm.

was obtained. Since the rate for the section of the nerve between the level of the injury and the brachioradialis could not be calculated, that of 1.9 mm per day has been employed in calculating  $t^1$  in all cases. The initial delay may be calculated from the latent period and  $t^1$ . This was done in 15 cases, and the values are given in table 5. In the absence of additional cases of suture from which to obtain a more

TABLE 5—*Values for Initial Delay in Regeneration in Fifteen Cases of Injury to Radial Nerve*

Nature of Injury	Level of Injury, Cm	Infection *	Scarring *	Initial Delay, Weeks	First Contraction, Weeks	Last Contraction, Weeks	Difference
<b>Axonotmesis</b>							
Simple fracture							
Case 77	10.0	Nil	Nil	9.8	16	27	11
Case 161	10.0	Nil	Nil	6.8	13	28	15
Case 317	10.0	Nil	Nil	9.8	16	29	13
Gunshot wound							
Case 185	12.0	Nil	Nil	6.3	14	30	16
Case 203	9.0	Nil	Nil	14.6	20	31	11
Case 255	2.0	I	S	8.0	8	26	18
Case 264	1.0	Nil	S	12.9	14	34	20
Gunshot wound + fracture							
Case 231	12.5	I	S	32.0	40	56	16
Case 118	9.0	I	S	10.6	16	28	12
Case 100	7.5	I	S	17.0	23	32-36	9-13
Case 106	5.0	I	S	14.6	17	36	19
Case 258	5.0	I	S	15.6	18	37	19
<b>Suture</b>							
Laceration							
Case 282	12.5	Nil	Nil	14.0	22	45	23
Case 180	4.0	Nil	S	16.6	20	42	22
Gunshot wound							
Case 40	5.0	I	S	15.9	20	40	20

\* I and S indicate significant infection and scarring, respectively

precise average rate of regeneration, that of 1.9 mm was employed in calculating the initial delay in the 3 cases of suture studied in the present investigation.

*Initial Delay Following Axonotmesis*—The level of the lesion has apparently no effect on the duration of the initial delay.

In general the variation in the calculated initial delays may be accepted as an expression of the relative severity of the injury in each case. The delay was, as a rule, of longer duration in cases in which the lesions were due to gunshot injuries, particularly when these were associated with compound fractures of the humerus and considerable infection and scarring. Cases 118, 185 and 255, however, are exceptions.

*Initial Delay Following Suture*—This varied from 14 to 16.6 weeks. The shorter interval (14 weeks) in case 282 could be attributed to the fact that the wound was clean and the nerve was not completely severed and was sutured at the time of the injury. In case 180 the nerve was sutured thirty-eight days after the injury, and,



though the wound was not infected, the residual scarring was considerable. In case 40 there was a considerable degree of infection of the wound in the initial stages and scarring, while secondary suture was not performed until eleven months after the injury. However, considering the complications operating in cases 40 and 180, the difference in the periods of delay is remarkably small. A possible explanation of this is that a well executed suture, in the absence of infection, converts the lesions in all cases into injuries of equivalent severity. The data in case 40 also indicate that a delay of eleven months before suture did not materially influence either the initial delay or the course of regeneration.

*Comment*—From the data available, it would appear that the duration of the initial delay is a measure of the severity of the nerve injury. In establishing this relationship, the observations in the simple fracture and suture groups were of particular significance.

In the simple fracture group infection and scarring were absent, and the roentgenographic and clinical data indicated that the nerve had been damaged at a corresponding level in all 3 cases. From the nature of the causative injury and the order and rate of regeneration which corresponded closely in all 3 cases, it appeared that the extent of the injury was similar and of minimal degree in each case. The initial delay was approximately 10, 10 and 7 weeks, respectively.

The course of regeneration in case 118, of the gunshot wound group, in which there were significant infection and scarring, closely resembled that observed in the simple fracture group. It seems reasonable to assume, therefore, that the extent of the injury in this case was similar and that infection and local scarring had provided no obstacle to regeneration.

Though the causative injury, the condition of the wound and the interval between the injury and the time of suture varied widely in the cases comprising the suture group, the course of regeneration corresponded fairly closely in the 3 cases. Here, disregarding the influence of infection and local scarring, the injury was known to be maximal in extent and the initial delays observed were 14, 15.9 and 16.6 weeks, respectively. The calculated initial delays in cases 100, 106, 203 and 258 approximated those in the suture group. Presumably, in these cases the injury was of greater severity than that observed in the simple fracture group.

Between these two groups will be found all intervening grades of severity of injury, which will account for intermediate variations in the initial delays. Thus, in cases of axonotmesis the severer the injury the closer will the course of regeneration approximate the sequence of events following suture.

The observed initial delay in case 231 was 32 weeks. This was the extreme maximum delay observed and was not approached in any other case. Its presence, however, is sufficient to indicate that delays beyond 17 weeks do occur.

Seddon, Medawar and Smith claimed that "there is no doubt whatever that the latent period after suture is longer than that after axonotmesis." An examination of the initial delays recorded in table 4 provides evidence that this is not invariably the case.

#### INFLUENCE OF DURATION OF LATENT PERIOD ON SUBSEQUENT COURSE OF REGENERATION

The course of regeneration subsequent to the onset of recovery may be expressed in terms of the time taken to reinnervate the entire pattern as measured from the onset of recovery in the first and the last muscle to recover. This period varied from 11 to 23 weeks. It was minimal in the simple fracture group and maximal in the suture group.

There are four possible explanations of the observed differences in the time taken to reinnervate the pattern.

- 1 The linear extent of the pattern is known to vary over wide limits in different persons. The recorded differences are of such magnitude that these alone could account for the observed differences in time.

- 2 The rate of regeneration may vary in different persons. It is extremely unlikely that the rate is a constant one, though the possible range of variations is unknown. It is improbable, however, that this factor alone would account for the observed differences in the time taken to reinnervate the pattern.

- 3 Some nerve fibers may be more severely damaged than others, and this may introduce a variation in the initial delay for different fibers. That this may occur has been deduced from the sequence of events following the injury in cases 27, 69, 99, 114, 202 and 244, in which the order of recovery was so deranged that the cases were discarded for the purposes of this investigation. To explain the variations in the time taken to reinnervate the entire pattern on this basis, the onset of regeneration in the fibers destined for either the first or the last muscle to recover, or both, must be delayed, though not in such a way as to disturb the normal serial order of recovery.

- 4 It may be that the over-all rate of regeneration is slower in cases in which the initial delay is longer, that is, in cases in which the injury has been more severe but in which it has, nevertheless, been equally distributed over all the fibers at the level of the injury.

If the duration of the initial delay is any guide to the severity of the injury, and there is some evidence to indicate that it is, then it

might justifiably be expected that initial delays of long duration would be associated with the longer periods taken to reinnervate the pattern. Reference to table 4 will show that in general this is so, particularly in the suture group, in which the injury is maximal in degree.

There are cases, however, which demonstrate that an early or late onset of recovery is not invariably followed by an accelerated or a retarded innervation of the pattern, respectively, such as might be expected had all the fibers been uniformly involved. If the severity of the injury were alone in question, then this evidence would indicate an injury of varying severity in individual fibers or fasciculi. The onset of regeneration must, then, have been unduly delayed in the fibers destined for either the first or the last muscle to recover or both, though without in any way disturbing the order of reinnervation (see paragraph 3).

The presence of so many variables makes it extremely difficult to assess the relative participation and contribution of each. Briefly, one or a combination of the following three factors may influence the time of reinnervation. Of these, the first was probably the most significant in the cases selected for this analysis:

(a) Variations in the linear extent of the pattern

(b) Variations in the severity of the injury with reference to the entire cross sectional area of the nerve or to individual fibers or fasciculi composing it

(c) Variations in individual rates of regeneration

#### ESTIMATION OF PERIOD IN WHICH RECOVERY SHOULD APPEAR

The time when recovery, spontaneous or following suture, should make its appearance can be calculated from the following information:

1 With injuries (axonotmesis) which are minimal in degree and usually due to uncomplicated trauma, an initial delay up to approximately 10 weeks may be expected. If the lesion is more severe, as it is after suture or after severe gunshot wounds associated with fracture of the humerus, infection and extensive scarring, then a delay of about 4 months may be expected in all but the exceptional cases.

Seddon, Medawar and Smith<sup>3</sup> concluded, on the other hand, that an interval of 6 to 8 weeks is an "unduly long latent period." It would seem, however, that this delay is too short and would account for only certain minimal injuries.

2 When the level of the lesion is known, the time taken for the regenerating axons to cover the distance from the site of the injury to the brachioradialis or the extensor carpi radialis longus may be calculated at an average rate of 1.9 mm per day.

In general, for a lesion situated 10 cm above the epicondyle, the onset of recovery in the brachioradialis should not be delayed beyond approximately 4 months after "simple" injuries and 6 months after severe injuries or nerve suture. Admittedly, it is difficult to distinguish between simple and severe nerve lesions, since the nature and severity of the causative injury are by no means an invariable guide. However, as previously shown, lesions are as a rule more severe when due to gunshot injuries, when the wounds are infected, when there is considerable scarring or when the humerus is fractured.

Delays of 6 months do not adversely affect the subsequent course of regeneration or apparently that following suture when this is indicated. The maximum latent period observed before spontaneous regeneration became evident and proceeded to completion was 10 months, though such a delay must be unusual. In the majority of the cases spontaneous regeneration was well advanced at the end of 6 months and ultimately proceeded to complete restoration of function.

By adding from 11 to 23 weeks, according to the type and severity of the nerve lesion, to the date of onset of recovery in the first muscle to recover, it is possible to calculate the approximate time when voluntary contraction may be expected in the last muscle to be reinnervated. This time, of course, has no reference to the full restoration of function, which is not attained until several months, or even years, later.

It is not proposed to discuss the controversial issues regarding the time when nerves in which conduction is completely interrupted (though the morphologic state is unknown) should be explored, since this involves factors other than those within the scope of the present study. The following facts, however, have been established from this investigation.

- 1 The majority of such lesions regenerate spontaneously, with an end result which, even though it may not be complete recovery, is at least far superior to the result which could be expected from nerve suture.

- 2 In the majority of cases in which exploration of the nerve is demanded and undertaken irreparable damage to the nerve will be revealed.

- 3 Delay in the onset of regeneration for periods up to 10 months will not adversely affect the subsequent course of regeneration or apparently that following suture when this is indicated.

#### SUMMARY

Observations on the course and rate of regeneration of motor fibers following lesions of the radial nerve are described.

The end results in a series of 63 cases of such lesions, on which the observations are based, are briefly summarized

Reference is made to the significance of variations in the serial order of motor recovery

The pathologic character of the lesions is analyzed in terms of the course of regeneration

A method for estimating rates of regeneration of functionally mature motor fibers in human peripheral nerves is described. With this method, rates of regeneration have been calculated over proximal and distal segments of the nerve below the origin of the branch to the brachioradialis. The results indicate that there is a progressive diminution in rate as regeneration advances

In cases of axonotmesis mean rates of 1.9 and 0.8 mm per day were obtained for the proximal and distal segments of the nerve, respectively. In cases of suture, mean rates of 1.2 and 0.6 mm per day were obtained for the proximal and distal segments of the nerve, respectively

Observations were made on the period intervening between the injury and the time when regenerating axons enter the distal segment—the initial delay—in cases of axonotmesis and suture

(a) The duration of the initial delay is a measure of the degree of severity of the injury

(b) The relationship of the duration of the initial delay to the reinnervation of the motor field subsequent to the onset of recovery is discussed in some detail. In general, initial delays of long duration are associated with longer periods for the reinnervation of the motor field. An early or a late onset of recovery is not, however, invariably followed by a subsequent accelerated or retarded rate of recovery

(c) An initial delay of up to 10 weeks may be expected in cases of injuries which are minimal in degree and which are usually due to uncomplicated trauma. If the lesion is more severe, as it is after suture or after severe gunshot wounds associated with a fracture of the humerus, infection and intensive scarring, then a delay of approximately 4 months may be expected. It is, however, difficult to distinguish between simple and severe nerve lesions, since the nature and severity of the causative injury are by no means an invariable guide

From a knowledge of the presumed initial delay, the level of the lesion and the rate of regeneration, it is possible to ascertain when recovery, spontaneous or following suture, should be expected

By adding 11 to 23 weeks, according to the type and severity of the nerve lesion, to the date of onset of recovery in the first muscle to be reinnervated, it is possible to calculate the approximate time when

voluntary contraction may be expected in the last muscle to be reinnervated

The maximal period intervening between the injury and the onset of recovery—latent period—before spontaneous regeneration became evident and proceeded to completion was 10 months. In the majority of nerves regenerating spontaneously, however, recovery had appeared at the end of 6 months.

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# ELECTRIC SHOCK THERAPY OF ELDERLY PATIENTS

CAPTAIN FRED FELDMAN  
AND  
LIEUTENANT SAMUEL SUSSELMAN  
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THE TREATMENT of elderly patients by means of electric shock constitutes one of the serious problems of this form of therapy. The problem centers about the difficulty of deciding whether the mental illness is sufficiently severe to warrant treatment in the face of physical handicaps. Many patients over 65 show no gross physical defects, others manifest various degrees of cardiovascular-renal impairment which increase the hazards of treatment significantly. The present

TABLE 1—*Distribution of Patients by Age and by Year of Treatment*

Age Group, Yr	1941	1942	1943	1944	Total No
65-69	5	4	14	12	35
70-74		1	6	5	12
75-79		1		3	4
80-82				2	2
	5	6	20	22	53

study considers a series of 53 patients each over 65 years of age who have been given electric shock therapy at the Albany Hospital during a period of three and one-half years. An attempt is made to evaluate the indications and contraindications for treatment, as well as the results and complications in this series.

## CASE MATERIAL

*Incidence*—Table 1 presents the distribution of the patients by age and by year of treatment. It will be noted that in 1941 and 1942 only 5 and 6 patients, respectively, over 65 were treated. In 1943 the figure increased to 20, and during 1944, 22 patients were treated. Thirty-five of the patients were in the age group from 65 to 69, 12, in the group from 70 to 74, 4, in the group from 75 to 79, and 2 were 82 years of age.

*Diagnosis*—The distribution of patients according to diagnosis is presented in table 2. The majority of the patients were listed as suffering from a depres-

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sion, 36 falling in this category. There were, in addition, 4 with manic states, 7 with psychoneuroses and 6 with paranoid psychoses. The condition of the depressed patients was chiefly designated as involutional melancholia, but 6 of them possessed a sufficient cyclothymic background to be considered as having a manic-depressive depression. The majority of the depressed patients had no previous history of mental illness, but 8 of them required a second or still additional series of treatments in the course of the three and one-half years covered by this survey. One patient has had four such series within three years, with a total of more than forty electroconvulsive treatments, showing fair to good recovery from her depression at each episode. There were reactive or situational factors in several cases.

There were 4 patients whose condition was diagnosed as manic-depressive psychosis, manic type, 1 of whom had two attacks and another four attacks during a three year period. The paranoid psychoses of the 6 patients resembled closely the typical paranoid state of the involutional period. The 7 patients classified as having a psychoneurosis each manifested a degree of concomitant depression. One displayed severe hypochondriasis with a strong background of anxiety. The 6 other patients were designated as having severe anxiety states with features of depression.

*Physical Status—Cardiovascular Status* A patient was considered to show little or no cardiovascular impairment when no clinical signs of heart disease

TABLE 2—*Distribution of Patients by Diagnosis*

Diagnosis	Number
Depression	36
Manic psychosis	4
Psychoneurosis with depression	7
Paranoid psychosis	6

were apparent, the electrocardiogram was normal and the blood pressure was below 160 systolic and 100 diastolic. Twenty patients were found to fulfil these criteria. The remaining 33 patients showed various grades of cardiovascular defect, from uncomplicated hypertension to actual heart failure, including pulmonary edema and auricular fibrillation. The most common indication of cardiac decline was electrocardiographic evidence of myocardial damage of some degree.

The patient with the most severely injured heart was a 65 year old woman suffering from severe depression and hypochondriasis, whose condition was diagnosed in December 1941 as auricular fibrillation with mild failure of the right side of the heart. Her electrocardiogram revealed "sinus arrhythmia with shifting pacemaker, left axis deviation and frequent ectopic ventricular beats." She was given nine electroconvulsive treatments, without complication, and was discharged as somewhat improved, to return for ambulatory treatment. She returned to the hospital in February 1944, again severely depressed, but a heart attack five months previously had rendered her physical condition so precarious that further electrotherapy was deemed inadvisable at this time. Because of her extreme agitation and depression, she was returned to the hospital in March 1944 and given two electroconvulsive treatments, after which she became dyspneic and pulmonary edema developed. The electric shock treatment was discontinued, and the patient rallied under supportive treatment. She was discharged with her psychiatric condition unimproved.



Several patients showed clinical and roentgenographic evidence of a moderately enlarged heart, and at least 2 had a greatly enlarged heart. Electrocardiograms revealed pronounced left axis deviation in several instances. The electrocardiographic reports also included such descriptions as "diffuse myocardial damage," "left ventricular enlargement," "definite evidence of myocardial damage," "possible coronary disease" and "suspicious evidence of arteriosclerotic heart disease." One patient presented a history of coronary occlusion one year before, followed by full clinical recovery. Several patients with systolic blood pressures of over 200 mm were treated, including a 75 year old woman with a pressure of 270 systolic and 176 diastolic.

None of these patients gave clinical evidence of progression of the cardiovascular impairment as a complication of therapy. On 2 patients electrocardiograms were taken both before and immediately after an electroconvulsive treatment. One of these patients showed no significant change, revealing the same moderate degree of myocardial damage after treatment as before. The second patient also presented some evidence of myocardial damage before electroconvulsive treatment but showed "improvement in the condition of the heart muscle" immediately afterward.

Although cardiovascular impairment was by far the most important finding in the physical examination, several patients displayed other physical defects. A 67 year old woman suffered from tic douloureux in 1940, and section of the trigeminal nerve was performed. She subsequently had staphylococcic meningitis, which cleared after intensive treatment, but she was left with residual paralysis of the left leg, weakness of the right leg and incontinence of urine. Roentgenograms of the lumbar portion of the spine revealed extensive destruction of the joints between the bodies of the first and second lumbar vertebrae and between the twelfth dorsal and the first lumbar vertebrae, with prominent kyphosis. She became severely depressed after her return home and, after a considerable period of unavailing treatment, was given several courses of electroconvulsive therapy, at first with erythroidine, a curare-like drug, and later without. She made a good, but not lasting, recovery each time, receiving about forty treatments altogether, without impairment of her physical condition.

Another patient, a man aged 72, had a dorsal kyphosis, which prevented any significant degree of extension of the thoracic portion of the spine. A third patient, a man of 67, showed small bilateral inguinal hernias. A woman of 70 had a 4 plus Wassermann reaction of the blood, with a negative reaction of the spinal fluid. Asthma, with signs of emphysema, was present in a man of 65. A man of 82 had a large ventral hernia. In none of these patients did untoward physical results appear.

*Duration of Treatment*—The average stay in the hospital for this group of patients was twenty-three days, with a range of from six to forty-two days. The number of electric shock treatments administered averaged about six per admission. The usual procedure following admission was a physical study of the patient, special care being devoted to an evaluation of the cardiovascular status. Treatment was therefore delayed for from three to seven days while roentgenograms and electrocardiograms were obtained, and medical consultation was requested when indicated. When begun, electroconvulsive treatments were given on a schedule of three times a week. A generalized grand mal seizure was obtained in each treatment. However, it was found necessary, somewhat more frequently than for younger patients, to space treatments more widely (i. e., twice a week) because of the confusion accompanying therapy.

Several patients quickly showed intellectual deterioration, necessitating cessation of treatment at an early stage. These were the patients in whom it had proved difficult to determine the degree of dementia as compared with the degree of depression and who were given treatment as a last resort. One patient showed a rapid decline in memory and comprehension after only two electroconvulsive treatments. Another patient, aged 77, became more agitated and confused with each succeeding convulsive treatment and was given a rest of ten days after the first two treatments, but manifested even more severe agitation when treatments were resumed. Therapy was therefore discontinued after four shocks. A third woman, aged 70, had a similar clinical course and showed extreme agitation after six electroconvulsive treatments.

On the other hand, a small number of patients showed gratifying response with as few as two to six electroconvulsive treatments. The oldest patient in the group, a man of 82, recovered completely from a severe depression after only two treatments. He became depressed again two months later, returned to the hospital and was discharged after only two electroconvulsive treatments, without untoward results. The longest course of treatments for a single admission was twelve, resulting in definite improvement. Several patients, however, were readmitted several times, 2 patients each receiving more than thirty electrocon-

TABLE 3—*Outcome of Electric Shock Therapy*

	For 43 Patients Admitted Only Once	For 10 Patients with Multiple Admissions (Total 24)	For Entire Group (53 Patients, 67 Admissions)
Recovery	10	4	14
Much improvement	16	9	25
Improvement	9	10	19
No improvement	8	1	9
	43	24	67

vulsive treatments, over a period of about sixteen months. These included ambulatory electric shock treatments, in addition to treatment in the hospital.

*Outcome*—Of the series of 53 patients, 43 were admitted only once, whereas 10 required two or more courses of treatment. The outcome of treatment for each group is indicated in table 3. In the group of patients with single admissions, it will be noted that 35 patients showed some degree of improvement, most of them falling in the category of those whose condition was "much improved." A patient was considered as "recovered" when both physician and family judged that he was as well after treatment as he had been before his illness and was able to resume his responsibilities in every sphere. A patient's condition was designated as "much improved" when he made an almost complete readjustment but still required an occasional psychiatric check-up. The condition was said to be "improved" when the patient was able to return home and make a partial social adjustment but was still incapable of assuming more than fractional responsibilities and still demanded considerable psychiatric care. The condition was designated as "unimproved" when the patient required commitment to a state hospital because of the palpable failure to mend. In most instances the diagnosis in the last group had been difficult because the degree of intellectual deterioration as compared with the magnitude of depression was impossible to estimate. The electric shock therapy, however, made the dementia more apparent, whereas at the same time the patient's behavior failed to improve.

The 10 patients who required multiple admissions showed a similar curve of improvement except that it was more heavily weighted in the range of those who were "much improved" and "recovered." None of this group was committed to a state hospital after the last admission in which electrotherapy was given, and most of them were discharged as at least "much improved." The number of admissions ranged from two, for the majority, to four, for several patients. The intervals between admissions extended from one to twelve or more months. In the entire group of 53 patients, with 67 admissions, 56 admissions, or 83.5 per cent, terminated with the patient's being pronounced "recovered," "much improved" or "improved."

When the outcome of treatment is viewed from the standpoint of diagnosis, it is evident that all groups show both successes and failures (table 4). The number of patients in each category outside the depressions is too small to permit the drawing of conclusions, but in each class of patients except those with paranoid psychoses the majority showed evidence of improvement. Of the 6 paranoid patients, 3 showed improvement and 3 were not improved. The

TABLE 4—*Final Outcome According to Diagnosis*

	Depres sion	Psycho neurosis	Manic State	Paranoid Psycho- sis
Recovery	11	1		
Much improvement	15	1	2	2
Improvement	4	5		1
No improvement	6		2	3
	<hr/> 36	<hr/> 7	<hr/> 4	<hr/> 6

8 patients who recovered all presented depressions of varying severity, and only 6 in the group of depressed patients required commitment.

*Complications*—There were no serious complications of treatment in the entire series except for the patient aforementioned who manifested congestive heart failure with auricular fibrillation before treatment and who became worse as the electroconvulsive treatments proceeded. All the other patients were discharged in as sound a physical condition, so far as could be discerned, as they displayed on admission. One patient had a questionable fracture of one rib. No significant difference between this group of elderly patients and younger patients was disclosed with respect to recovery from the seizure. There were, however, several occasions when artificial respiration was necessary, and 1 patient showed sufficiently severe respiratory difficulties after the second convulsive treatment to warrant discontinuing the treatments. There was no increase in the number of complaints about soreness of the back, and in no case was this complication severe enough to require roentgenographic examination of the spine. One patient complained for several days of moderate soreness of one arm.

Several patients regularly evinced excitement after the seizure, but this was controlled, as in younger patients, by intravenous injection of sodium amytal, in a dose of  $4\frac{1}{2}$  grains (0.29 Gm.)

#### COMMENT

The voluminous literature on electric shock therapy carries many scattered references to the treatment of aged patients, but few detailed

reports are available. Cash and Hoekstra<sup>1</sup> (1943) reported on a group of 84 patients with affective disorders, of whom 4 were over 70 and 10 over 60 years of age. Of this group, 64 per cent recovered, and 35 per cent showed social remissions with residual symptoms. The patients were treated with curare, without traumatic complications. No special reference to the cardiovascular status of the patients was made except for the statement that "the best results are obtainable in the older age groups, and complications are of no greater incidence than in the younger patients." The author noted, also, that treatment should not be withheld when disease of the coronary arteries is present unless there is evidence of cardiac decompensation.

Evans<sup>2</sup> reported on the treatment of a series of patients 17 of whom were over 60 and 5 over 70 years of age. The proportions of this group given electric and metrazol shock therapy are not stated. The author mentioned the case of a 74 year old woman with electrocardiographic evidence of complete left bundle branch block who responded well to twenty electric shock treatments. Two women over 60, with systolic blood pressures over 200, were successfully treated. Kline and Fetterman<sup>3</sup> reported on electrocardiographic studies of a group of 42 patients of whom 5 were over 60 and 1 was over 70. Electrocardiograms were taken before and after induction of a major convulsion. There were 5 patients in the series with abnormal cardiovascular systems, of whom 3 had hypertension, but none showed electrocardiographic abnormalities before or after treatment. A fourth patient was a 55 year old woman whose "angina pectoris" had been treated by the surgical establishment of a collateral coronary bed. She, too, showed no electrocardiographic alteration. The fifth case was that of a man aged 58 with rheumatic valvular disease and cardiac enlargement.

Kalinowsky<sup>4</sup> discussed electric shock therapy, mentioning 1,500 cases but did not mention age as a contraindication. Evans<sup>5</sup> studied 50 patients over the age of 50 who had had one or more convulsions induced either by metrazol or by electric shock, of this group 17 were over 60 and 5 over 70. It has been our experience that patients between 50 and 65 years of age may be validly considered to fall in the same

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1 Cash, P. T., and Hoekstra, C. S. Preliminary Curarization in Electric Convulsive Shock Therapy, *Psychiatric Quart* **17** 20-34, 1943.

2 Evans, V. L. Physical Risks in Convulsive Shock Therapy, *Arch Neurol & Psychiat* **48** 1017 (Dec) 1942.

3 Kline, E. M., and Fetterman, J. L. Electrocardiographic Changes Following Electrically Induced Convulsions, *Am Heart J* **24** 665-670, 1942.

4 Kalinowsky, L. B. Electric Convulsive Therapy with Emphasis on Importance of Adequate Treatment, *Arch Neurol & Psychiat* **50** 652-660 (Dec) 1943.

5 Evans, V. L. Convulsive Shock Therapy in Elderly Patients. Risks and Results, *Am J Psychiat* **99** 531-533, 1943.

category as young and middle-aged patients so far as risks of treatment are concerned. In the 50 to 65 year group, the hazards of treatment are apparently not significantly raised, and the expected results approximate those found in the lower age groups. In patients over 65, however, the proportion of persons with cardiovascular impairments, manifest or latent, is so high that each patient becomes a problem in which the cardiovascular threat to life when the treatment is given must be weighed against the magnitude of the mental illness.

*Diagnosis Problem of Determination of Intellectual Impairment —*

The cardinal problem in diagnosis is to ascertain whether there is present any true senile intellectual impairment and to determine the magnitude of this impairment. Patients suitable for treatment are those with definite psychotic elements of depression, mania or the paranoid state who do not show any appreciable degree of senile dementia. The differentiation between the retardation of depression and the dulness of dementia is sometimes difficult. The delay in the responses of the depressed patient may be misinterpreted and taken for inability to comprehend the questions asked. If care and patience in appraising the intellectual resources are exercised, however, it can be demonstrated that memory, orientation and reasoning are unimpaired. We have found useful a simple memory test developed in this hospital<sup>6</sup> whereby gross defects in remembering may be detected within a few minutes.

If the patient is stuporous, or so mute and underactive that the presence of intellectual defect cannot be determined, it is possible to allay this condition by means of an intravenous injection of sodium amytal. This drug, injected in amounts of from 1 to 8 grains (0.065 to 0.52 Gm.) serves in the majority of cases to break through the retardation and to elicit adequate responses to allow evaluation of memory and orientation. Information evoked in this way should be weighed in conjunction with the data supplied by the informants. It may be impossible to ascertain definitely whether or not a mild degree of senile dementia is present in addition to the more acute depression, the decision for or against treatment should be made with reference to the condition of the patient before the onset of the acute phase of the present illness. If there had been good adjustment, a chance taken to return to this status would seem desirable.

It was noted in the section devoted to the duration of treatment that several patients displayed definite intellectual deterioration after only two or three electroconvulsive treatments. The difficulty in evaluating the mental status is demonstrated in the following cases.

An agitated patient aged 75 had a disorder diagnosed as both paranoid and intellectual dementia. The weight of each factor could not be satisfactorily

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6 Feldman, F, and Cameron, D. E. The Measurement of Remembering, *Am J Psychiat* **100** 788-791, 1944

assayed before treatment. She had shown mental changes over a period of about ten years, in the form of seclusiveness, negativism and paranoid trends, and just before admission had become untidy, noisy, destructive, obscene, confused and disoriented. In the hospital the patient was so overactive and assaultive that no appraisal of her orientation and memory was feasible. She was given a series of electric shock treatments, in response to which she became much quieter and eventually fairly tractable. However, it became obvious that there were significant changes in the direction of dementia, shown in her persistent disorientation and confusion, and it was finally considered advisable to transfer her to a state hospital.

A second patient, a man of 70, entered the hospital with severe depression, marked by the delusion that the milk produced on his farm was poisonous. Evaluation of his mental status seemed to reveal, in addition to the melancholia and delusions, a significant degree of confusion, disorientation and impairment of memory. It was not possible to gauge the amount of dementia, however, because of his retardation, and electroconvulsive therapy was instituted, the risks and prognosis having been explained to the family. After seven electroconvulsive treatments the depression lifted, the delusions disappeared and it was possible to determine that the patient's intellectual resources were very good indeed. He was discharged to return home as much improved.

*Effectiveness of Treatment*—The value of treatment is seen in the high proportion of patients returned to their homes as either recovered or much improved. The figures for improvement compare favorably with those obtained in the treatment of younger patients with similar conditions, especially the depressions. The paranoid states responded least well, with 3 failures among 6 patients. The psychoneuroses did not show complete recovery, but in the majority of instances significant improvement occurred. A woman aged 68 showed few elements of true melancholia but presented a twenty year history of severe hypochondriasis, having undergone eight major operations. During the few weeks before admission she had become increasingly tense and had begun to fear that she might become mentally ill. She was agitated but in good contact and constantly recounted her illnesses, with a painful fidelity to detail and usually with visible enjoyment. She improved significantly with electric shock treatment and was able to return to her household.

*Hospital Care of Patients*—In general, elderly patients pose the same problems as younger patients with similar conditions except that they must be examined frequently and with especial care for signs of heart failure. The degree of agitation in this series of patients was variable, but in several the overactivity was so great that constant restraints and sedation were necessary to prevent self injury and exhaustion. Feeding became a major problem at times, and administration of nourishment by means of gavage or clysis was often inadequate before shock treatment was instituted. A number of patients constituted suicide risks, and the usual precautions were taken. The

patients were urged to be up and about and were kept busy about the ward when possible

*Complications of Therapy*—It has been noted that no complications resulted in the present series except for increased cardiac failure in 1 patient. The hazards of electric shock therapy in elderly patients, the literature on which was reviewed at the beginning of this section, can be seen to be concerned primarily with cardiac involvement. The cardinal problem from the standpoint of complications is that of the probability of death with mounting age. This question is discussed in the next section of this paper.

Among other complications, one would expect a greater frequency of fractures in elderly patients, but no reliable data on this score were discovered in the literature, and no fractures occurred in our series except for a questionable fracture of a rib. The possibility of increased danger in elderly patients during the period of respiratory depression immediately following the convulsion is suggested by the fact that 1 patient in this series experienced sufficiently severe respiratory difficulties after her second seizure to make further treatment inadvisable. Again, it should be stressed that the risks must be balanced against the possible benefits.

*Association of Age with Fatalities from Electric Shock Therapy*—No deaths occurred among the elderly patients in our series. It was thought worth while, however, to survey the literature for deaths associated with electric shock therapy in order to determine the role of advanced age.

There is reference in the literature<sup>7</sup> to 19 deaths attributed to electric shock therapy, and to this number may be added a fatality occurring in this hospital. Many of the reported cases are not well documented, and in at least 3 cases death took place more than a month after the last treatment. If these cases are excluded from

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7 Hamsa, W. R., and Bennett, A. E. Traumatic Complications of Convulsive Shock Therapy, *J. A. M. A.* **112** 2244-2246 (June 3) 1939. Hayman, M., and Brody, M. W. Metrazol Therapy in Schizophrenia. Report of a Fatal Case with Autopsy, *ibid.* **112** 310-311 (Jan 28) 1939. Heilbrunn, G., and Weil, A. Pathologic Changes in the Central Nervous System in Experimental Electric Shock, *Arch. Neurol. & Psychiat.* **47** 918-930 (June) 1942. Hoffman, M. G., Sandler, N., and Hecht, H. Paroxysmal Auricular Fibrillation Complicating Metrazol Shock Therapy, *Am. J. Psychiat.* **97** 372-379, 1940. Impastato, D. J., and Almansì, R. A Study of Over Two Thousand Cases of Electrofit-Treated Patients, *New York State J. Med.* **43** 2057-2064, 1943. Androp, S. Electric Shock Therapy in the Psychoses, *Psychiatric Quart.* **15** 730-749, 1941. Bellet, S., Kershbaum, A., and Furst, W. The Electrocardiogram During Electric Shock Treatment of Mental Disorders, *Am. J. M. Sc.* **201** 167-177, 1941. Cleckley, H., and Egleston, Du B., Jr. Some Observations on Cardiovascular Changes in Shock Therapy, *Psychiatric Quart.* **15** 662-679, 1941.

consideration, the remaining 17 cases may be somewhat arbitrarily divided into three categories, as outlined in table 5. It must be stressed that this classification is a rough one, designed only to throw light on the degree of cardiac origin of electric shock fatalities. With this reservation in mind, it may be said that the first category includes those cases, numbering 9, in which the death was definitely or probably imputed to cardiac involvement. The second category consists of 7 cases in which either clinical or postmortem evidence was insufficient to reveal the probable cause of death but in which, so far as can be appraised from the reports, it may conceivably have been cardiac. The third category includes a single case of death ascribed to pneumonia.

In only 3 of the 17 cases enumerated was the patient over 65 years of age, and all have been placed in the first of the three aforementioned categories—i.e., cases in which the death was probably of cardiac origin. The distribution of ages for the 17 cases is indicated in column 2 of table 5, the 3 patients over 65 were 70, 70 and 75. It

TABLE 5—Cause of Fatalities Associated with Electric Shock Therapy  
Seventeen Cases

	Number	Age							
		?	23	42	57	61	70	70	75
Death definitely or probably due to cardiac failure	9	?	23	42	57	61	70	70	75
Cause of death questionable, conceivably due to cardiac failure	7	?	29	35	45	47	50	58	
Other causes	1	59							

will be seen that the ages in the remaining 6 cases in the first category, in which death was probably of cardiac origin, range from 23 to 61. None of the 6 patients was considered a bad risk on the basis of pretreatment clinical studies, whereas the 3 patients over 65 were thought to present greatly increased risks.

The number of deaths is too small for the derivation of sweeping conclusions, but it may be seen that the number of deaths of patients over 65, 3 among 17, should not be an overwhelming deterrent. This number may be contrasted with the figure of approximately 5 per cent for the group over 65 years of age in a large series of patients of all types who received electric shock therapy. (In the Albany Hospital, over the past three and one-half years, more than 1,000 patients have received electric shock therapy, among whom are included only 53 patients over 65.) It is probable that the figure of 5 per cent may be somewhat too large to apply to the population of the country as a whole. Contributing to lower this figure is the fact that many of the large series reported have included, exclusively or predominantly, schizophrenic patients, who fall principally into the lower age groups.



Ebaugh, Barnacle and Neubuerger<sup>8</sup> collected data on 7 cases of death associated with electric shock therapy and added 2 of their own. The ages of 6 of the 9 patients were between 45 and 58 years. One patient was 29, and the remaining 2 were 75 and 79 respectively. Both the patients from their own series were 57 years of age, and the deaths of both were attributable to cardiac impairment. One of these patients presented no clinical or electrocardiographic evidence of cardiac impairment but died of coronary thrombosis one and one-half hours after the twelfth grand mal seizure. The second patient, also, showed no clinical evidence of heart disease, and death may have been due to a severe vagotonic reaction, with cessation of both cardiac and respiratory activity. Of the 7 patients 3 died one to four months after treatment and the other 4 within three days after a treatment. The 3 patients whose deaths occurred after more than a month were 45, 56 and 79 years of age. The patients aged 45 and 79 were noted to have died of "cardiac failure." The patient aged 56 died three months after treatment, of "acute infection of the respiratory tract and septicemia."

The 4 patients dying within three days after a treatment are of more immediate interest. On 3 of these patients, aged 29, 50 and 58 respectively, no autopsy was performed, and the designated causes of death, namely, "coronary thrombosis and influenza," "involvement of central nervous system, preceded by respiratory failure" and "failure to regain consciousness," are necessarily vague. The last of these 4 patients, a man aged 75, died immediately after the third treatment, with cardiac fibrillation. There had been a pretreatment clinical diagnosis of advanced generalized arteriosclerosis, and this was confirmed at autopsy.

Jetter<sup>9</sup> reported 3 cases of death caused by electric shock administered to patients with diseased hearts. Of these patients, 1 was 23, the second 61 and the third 70. In the 23 year old patient autopsy showed acute focal nonsuppurative myocarditis and acute glomerulonephritis, both probably of several days' duration. The relationship between the electric shock, the eighth in the second series, and death was not clear, inasmuch as heart failure appeared only several hours after the treatment, and death occurred twelve or sixteen hours afterward. The second patient, a man of 61, died ten minutes after the eighth treatment, in severe circulatory collapse. Physical examination had disclosed no outstanding abnormalities, the size of the heart being normal, the rate regular and the blood pressure 156 systolic and 90 diastolic. Apparently, no electrocardiogram was taken. Postmortem observations included

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8 Ebaugh, F. G., Barnacle, C. H., and Neubuerger, K. T. Fatalities Following Electric Convulsive Therapy. Report of Two Cases with Autopsy, *Arch Neurol & Psychiat* **49** 107-117 (Jan) 1943.

9 Jetter, W. W. Fatal Circulatory Failure Caused by Electric Shock Therapy, *Arch Neurol & Psychiat* **51** 557-563 (June) 1944.

extensive obliterating coronary arteriosclerosis and recent myocardial infarct. The third patient, aged 70, presented a sufficiently severe depression to warrant treatment in face of the known diagnosis of hypertensive vascular disease, cerebral thrombosis and old coronary thrombosis with bundle branch block. The electrocardiogram showed disease of the coronary arteries and left frontal bundle branch block. Death occurred twelve minutes after the beginning of the sixth treatment. Another case of fatality due to cardiac failure following electric shock therapy was mentioned by Levy, the death being attributed by Jetter<sup>9</sup> to vagotonic action. The age of the patient was not stated.

Cash and Hoekstra<sup>1</sup> reported the death of a man of 47 two hours after his fifth electric shock treatment, with cure. Autopsy did not reveal the exact cause of death, although its cardiac origin was considered likely. There was conspicuous sclerosis of the anterior descending coronary artery. Ziegler mentioned a patient of "about 70" who died at an unstated interval after an electroconvulsive treatment and in whom autopsy showed a badly damaged myocardium. No other details were given. He mentioned, too, a man of 68 with a history of having had coronary thrombosis several years before who responded well to therapy. Gralnick<sup>10</sup> reported the deaths associated with electric shock of 2 patients, aged 35 and 45. One patient died one week after the fourteenth treatment, in status epilepticus, autopsy was not obtained. The second patient died two days after the second treatment, the cause being unascertainable at autopsy, although cerebrovascular syphilis was present.

The death occurring in our hospital was that of a 42 year old white woman who was admitted to the Albany Hospital in February 1942 with a history of severe anxiety and depression, together with delusions and hallucinations. Physical and neurologic examinations gave normal results except that the patient appeared poorly nourished. Laboratory data were within normal limits. A diagnosis of schizophrenia was made, and electroconvulsive therapy was started in February 1942. The first seizure was immediate but predominantly affected the right side at the onset, spreading, to involve the whole body, over a period of forty seconds. After the seizure the patient was apneic for thirty seconds and then resumed normal respirations. Two days later the second electroconvulsive treatment was given. The first stimulus produced only a petit mal attack but was repeated with increased voltage, resulting in a grand mal seizure which lasted twenty-five seconds, and followed the same pattern as that on the first day. After the convulsion a few breaths were taken spontaneously, and then respiration stopped. The pulse

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<sup>10</sup> Gralnick, A. Fatalities Associated with Electric Shock Treatment of Psychoses, *Arch Neurol & Psychiat* 51 397-402 (April) 1944

became slow, and, despite artificial respiration, intravenous injections of metrazol and intracardiac administration of epinephrine, the patient died. Permission for autopsy could not be obtained.

#### SUMMARY

The results of electric shock therapy in a group of 53 patients aged 65 or more are reported. The difficulties in diagnosis, the contraindications to treatment and the complications and effectiveness of therapy are discussed. Three cardinal problems have emerged from this study.

1 The differentiation of true intellectual decline and other types of psychoses of the senium, especially depression, must be made. Suggestions for making this distinction are offered.

2 The significance of an impaired cardiovascular system in the patient with serious mental illness must be evaluated in terms of what the future holds for the patient with and without treatment.

3 When a diagnosis other than senile dementia can be made in a patient over 65, especially that of depressive, manic or paranoid psychosis, electric shock therapy should be considered. The only contraindications should be extreme defects in the physical state, particularly in the cardiovascular system.

Albany Hospital

## PATTERN OF METABOLIC DEPRESSION INDUCED WITH PENTOTHAL SODIUM

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THE INTRAVENOUS administration of pentothal sodium, an ultra-short-acting barbiturate, is used extensively for the production of clinical anesthesia. The clinical manifestations of cortical depression are evident within thirty seconds after the initial injection. During the action of the drug the patient passes through several phases of depression, depending on the influence of the drug on the various cerebral areas. Brazier and Finesinger<sup>1</sup> have shown with the aid of the electroencephalograph a depressant effect of pentothal sodium on the several parts of the cortex. First the frontal area was depressed, then the parietal and, last, the occipital. It has been demonstrated *in vitro* that barbiturates exert an inhibitory effect on cellular respiration of the brain,<sup>2</sup> particularly in the parts of the brain with the highest oxygen intake, such as the more cephalic regions, which suffer the most pronounced metabolic retardation.<sup>3</sup>

The venous drainage of the cerebral hemispheres and of the basal ganglia is not the same in all persons. Though the blood from the lower part of the brain stem, including the midbrain and the medulla oblongata, as well as the cerebellum, is equally represented in the two internal jugular veins, the venous return from the upper portions of

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, Mrs Ilse Memelsdorff made the determinations of glucose and lactic acid

This investigation was aided by a grant from the Winthrop Chemical Company Research Fund

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1 Brazier, M A B, and Finesinger, J W. Action of Barbiturates on the Cerebral Cortex, *Arch Neurol & Psychiat* **53** 51-58 (Jan) 1945

2 Quastel, J H. Respiration in the Central Nervous System, *Physiol Rev* **19** 135-183, 1939

3 Himwich, H E, Sykowski, P, and Fazekas, J F. A Comparative Study of Excised Cerebral Tissues of Adult and Infant Rats, *Am J Physiol* **132** 293-296, 1941

the brain is not similarly arranged<sup>4</sup> In the majority of persons the blood from the greater part of the cerebral cortex appears chiefly either in the right or in the left internal jugular vein, after passing through the superior longitudinal sinus, while the blood from the sinus rectus, coming partially from the basal ganglia, goes to the opposite side Because of this arrangement of the venous drainage, it is possible to obtain blood from one internal jugular vein which is more representative of the cerebral hemispheres than is the blood of the opposite internal jugular vein, which, in turn, may be regarded as carrying the greater portion of the venous drainage from the basal ganglia In some persons, however, the contents of the superior longitudinal sinus are divided about equally between the right and the left lateral sinus In addition, a small percentage of persons possess a torcular Herophili, in which the return from the cerebral hemispheres and that from the basal ganglia are mixed In that case the two internal jugular veins are equally representative of the upper and the lower part of the brain

An opportunity to determine whether the cerebral hemispheres are depressed before other parts of the brain is made possible by the course of the cerebral venous return If, for example, the administration of a drug reduces the arteriovenous oxygen difference of the blood from the side carrying the cortical component more than that from the opposite side and the cerebral blood flow is not accelerated, the results would indicate that the cerebral hemispheres are the first part of the brain to be depressed by that drug Such results would cast light on the pattern of action of the drug used

#### METHOD

On 11 of 12 patients control observations were made by drawing successive samples of blood from both internal jugular veins and from the brachial artery, with the use of procaine anesthesia On another day pentothal sodium, in 1 per cent solution, was administered intravenously to each of these subjects, who had not received previous medication For the injection, a needle communicating with a two way stopcock was inserted into the antebrachial vein, thus permitting the injection of the pentothal solution in one of two ways either by syringe or by the intravenous drip method The initial injection was slow, irrespective of the source of pentothal sodium, and varied with each patient The solution was allowed to run at such a rate as to obtain any required level of depression

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4 (a) Gibbs, E L, and Gibbs, F A The Cross Section Areas of the Vessels That Form the Torcular and the Manner in Which Flow Is Distributed to the Right and Left Lateral Sinus, *Anat Rev* **59** 419-426, 1934 (b) Batson, O V Anatomical Problems Concerned in the Study of Cerebral Blood Flow, *Federation Proc* **3** 139-144, 1944 (c) York, G E, Homburger, E G, and Himwich, H E Similarity of the Cerebral Arteriovenous Oxygen Differences on the Right and Left Sides in Resting Man, *Arch Neurol & Psychiat* **55** 578-582 (June) 1946

and to retain it over a given period. If it was desired to lighten the anesthetic effect after the initial injection, the administration of pentothal sodium was slowed or stopped. For deeper stages of barbiturate depression the administration of the drug was continued and accelerated.

When the patient was in light surgical anesthesia, three needles with stylets were inserted and made secure with strips of adhesive tape, a 19 gage needle was placed in each internal jugular vein and a 20 gage needle in the femoral artery. As a result of this preparation samples of blood could be drawn simultaneously from the three vessels. This simultaneity is an essential step in a comparison of the arteriovenous oxygen differences for the right and the left side for any given time.

The samples of blood were collected in glass containers over mercury, as previously described,<sup>5</sup> and were analyzed immediately for oxygen and carbon dioxide by the method of Van Slyke and Neill.<sup>6</sup> Analyses checked to within 0.2 volume per cent, and variations of 1 volume per cent or less between the arteriovenous oxygen differences for the right and for the left side were within the experimental error. The amount of glucose was determined with the technic of Hagedorn and Jensen,<sup>7</sup> and the lactic acid content, according to the method of Barker and Summerson.<sup>8</sup> The samples for the determinations of glucose and lactate were measured from a 1 cc Van Slyke pipet. This procedure standardized the measurement of all samples of blood, whether for gases, glucose or lactic acid. Differences of 4 mg of glucose and 12 mg of lactate per hundred cubic centimeters were considered significant.

## RESULTS

*Oxygen*—In 11 resting patients the arteriovenous oxygen differences for blood from the two sides varied from 0.02 to 1.12 volumes per cent, with an average of 0.51 volume per cent, which is a value in agreement with the results of previous studies.<sup>4c</sup> After the injection of pentothal sodium two degrees of clinical changes were observed in the majority of patients, resulting in a classification of light and deep anesthesia. In light anesthesia the patients reacted to stimuli, whether their responses retained some voluntary element or were entirely involuntary. When the application of even painful stimuli failed to elicit muscular reactions, anesthesia was regarded as deep. In 17 of 22 observations at the lighter levels of anesthesia the arteriovenous oxygen differences for blood from either the right or the left internal jugular vein were preponderantly decreased. On 7 occasions the arteriovenous difference was decreased more on the right than on the left.

5 Himwich, H. E., and Castle, W. B. Studies in the Metabolism of Muscle. I. The Respiratory Quotient of Resting Muscle, *Am J Physiol* **83**:92-114, 1927.

6 Van Slyke, D. D., and Neill, J. M. The Determination of Glucose in the Blood and Other Solutions by Vacuum Extraction and Manometric Measurement, *J Biol Chem* **61**:523-573, 1924.

7 Hagedorn, H. C., and Jensen, B. N. Zur Mikrobestimmung des Blutzuckers mittels Ferricyanid, *Biochem Ztschr* **135**:46-58, 1923.

8 Barker, S. B., and Summerson, W. H. The Colorimetric Determinations of Lactic Acid in Biological Material, *J Biol Chem* **138**:535-554, 1941.

TABLE 1—Oxygen Content, in Volumes per Cent, of Cerebral Blood in Patients with Different Anatomic Patterns of Venous Return from Cerebral Hemispheres

Pa- tient No	Condi- tion *	Arteriovenous Oxygen Difference							Comment	
		Arterial Oxygen Content	Oxygen Content of Internal Jugular Venous Blood		Right Side	Left Side	Smaller on Left Than on Right			Equal on Two Sides
			Right	Left			Internal	Jugular		
A	Predominant	Component in	Right	Internal	Jugular	Vein †				
1	Control	18 22	12 24	11 12	5 98	7 10		1 12		
	Light	17 86	16 22	11 95	1 64	5 91		4 27		
	Light	17 17	13 67	11 84	3 50	5 33		1 83		
	Light	15 99	13 53	11 64	2 46	4 35		1 89		
	Deep	15 89	14 45	14 73	1 44	1 16			0 30	
	Deep	15 46	13 15	12 85	2 31	2 61			0 28	
2	Control	20 47	13 72	13 41	6 75	7 06			0 31	
	Light	19 65	16 50	13 61	3 15	6 04		2 89		
	Light	19 23	16 48	12 95	2 75	6 23		3 53		
	Deep	18 50	14 38	15 51	4 12	2 99	1 13			
	Deep		14 06	13 96					0 10	
	Deep	8 88	2 90	3 39	5 98	5 45			0 49	
3	Control	19 52	12 26	11 43	7 26	8 09			0 83	
	Light	18 35	12 94	10 18	5 41	8 17		2 66		
4	Control	18 94	11 22	12 11	7 72	6 83			0 89	
	Light	16 90	12 40	11 05	4 50	5 85		1 35		
B		Predominant	Component in	Left	Internal	Jugular	vein †			
5	Control	19 65	12 52	13 18	7 13	6 47			0 66	
	Light	18 12	12 95	14 02	5 17	4 10	1 07			
	Light	17 47	11 58	15 16	5 89	2 31	3 58			
	Light	16 33	10 53	14 18	5 80	2 15	3 65			
	Deep		12 60	12 94					0 34	
	Deep	7 27	6 26	6 56	1 01	0 71			0 30	
6	Control	17 33	10 23	10 21	7 10	7 12			0 02	
	Light	15 59	10 23	14 66	5 36	0 93	4 43			
	Light	15 29	11 53	15 00	3 76	0 29	3 47			
	Deep	15 72	9 83	10 52	5 89	5 20			0 69	
	Deep	13 45	11 97	12 97	1 48	0 45			1 00	
	Deep	6 37	2 93	3 71	3 44	2 66			0 78	
7	Control	18 29	11 71	11 31	6 58	6 96			0 38	
	Light	18 83	11 00	15 43	7 83	3 40	4 43			
	Light	18 80	10 04	16 76	8 76	2 04	6 72			
8	Light	16 82	12 67	15 22	4 15	1 60	2 55			
	Light	14 98	9 46	11 21	5 52	3 77	1 75			
9	Control	15 65	9 36	9 90	6 29	5 75			0 54	
	Light	14 21	8 11	11 41	6 10	2 80	3 30			
C		Equal Division	Between	Right and Left	Internal	Jugular	Vein §			
10	Control	19 78	10 72	11 21	9 06	8 57			0 49	
	Light	17 90	10 43	10 50	7 47	7 40			0 07	
	Light	17 08	10 97	10 88	6 11	6 20			0 09	
	Light	16 86	9 06	9 81	7 80	7 05			0 75	
	Deep	15 28	9 44	9 39	5 84	5 89			0 05	
11	Control	18 05	10 72	11 10	7 33	6 95			0 38	
	Light	17 73	10 99	11 65	6 74	6 08			0 66	
	Deep	13 01	10 71	10 35	2 30	2 66			0 36	
12	Control	19 24	12 36	12 31	6 88	6 93			0 05	
	Light	17 98	11 27	11 35	6 71	6 63			0 08	
	Deep	15 56	13 30	12 01	2 26	3 55	1 29			
	Deep	18 51	16 85	16 10	1 66	2 41			0 75	

\* 'Deep' and 'light' refer to levels of anesthesia

† Patients 1 to 4, listed in A, exhibited the cortical component of blood chiefly in the right internal jugular vein as evidenced by the smaller arteriovenous oxygen difference on the right side than on the left side in all observations made during light anesthesia. The values for patient 1 are typical of this group. The control arteriovenous oxygen difference on the right side is 5.98 volumes per cent, and the difference falls to 1.64, 3.50 and 2.46 volumes per cent during light anesthesia. The control on the left side is 7.10 volumes per cent, and the difference is comparatively better sustained, at 5.91, 5.33 and 4.35 volumes per cent. During deep anesthesia the differences do not vary significantly and are reduced to their lowest levels 1.44 and 2.31 volumes per cent on the right side and 1.16 and 2.61 volumes per cent on the left side.

(Footnotes continued on next page)

(table 1 A), in 10 determinations it was lowered more on the left than on the right (table 1 B), and in only 5 were the arteriovenous oxygen differences equal on the two sides (table 1 C) In 12 of 14

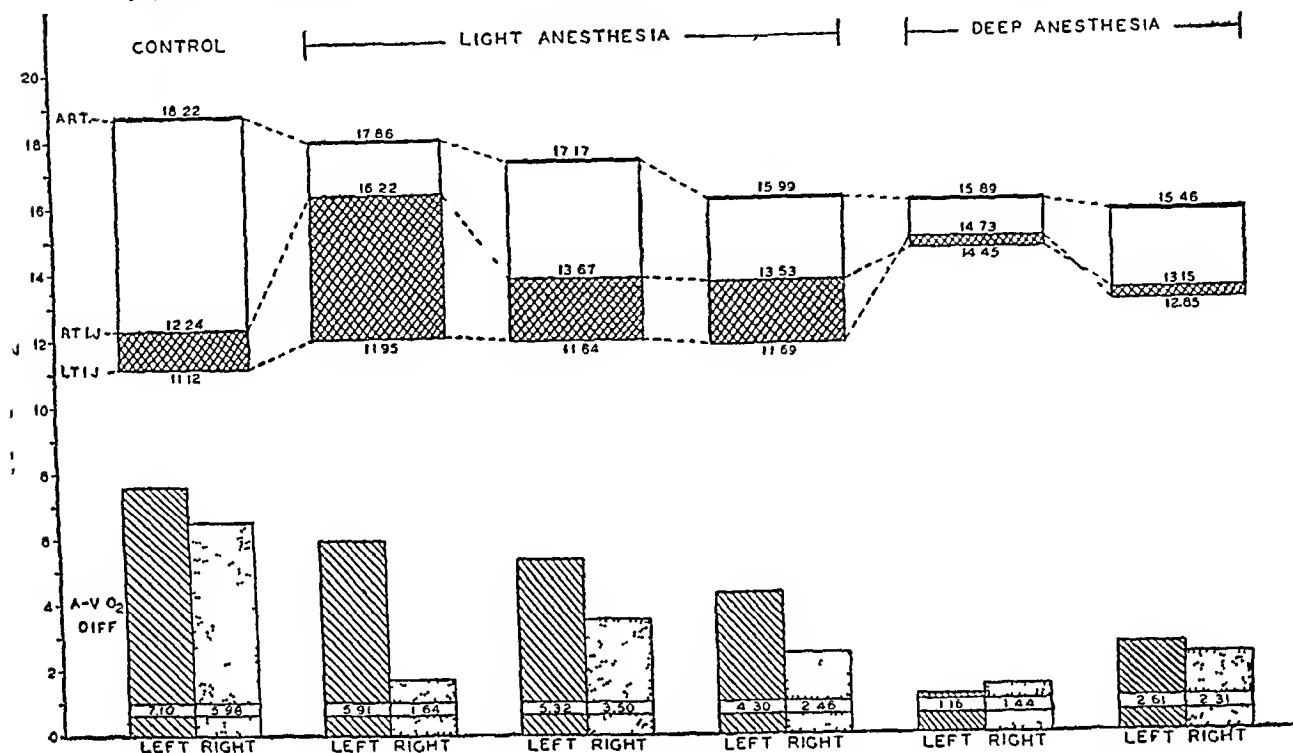


Fig 1—The results for patient 1 are illustrative of the group in which the major return of blood from the cerebral hemispheres appears in the right internal jugular vein. In all observations made on the subject during light depression, the arteriovenous differences on the right side were more reduced than those on the left side, while during deep anesthesia the differences on the two sides were at their lowest value and were in agreement with each other. The same data are presented in two ways. The columns in the lower part of the figure express the arteriovenous oxygen differences for the right and left sides in terms of volumes per cent, while in the upper portion are the actual values for the arterial and venous oxygen contents. The cross hatched area shows the difference in the oxygen content of the blood between the right and the left internal jugular veins. The gradual decrease of arterial oxygen is evident as the anesthesia becomes deeper.

#### FOOTNOTES TO TABLE 1

† In B are listed the results for patients 5 to 9, whose cerebral hemispheres are drained chiefly into the left internal jugular vein, as evidenced by the smaller arteriovenous oxygen differences on the left side than on the right when the subjects were under light anesthesia. Patient 5 typifies this group. The control arteriovenous oxygen difference on the left side is 6.47 volumes per cent and falls to 4.10, 2.31 and 2.15 volumes per cent during light anesthesia, while on the right side the control value is 7.13 volumes per cent and remains comparatively high, at 5.17, 5.89 and 5.80 volumes per cent. During deeper depression the arteriovenous oxygen differences are equal on the two sides and are within the experimental error. Note the progressive fall in the arterial oxygen content to the lowest value, 7.27 volumes per cent, during deep anesthesia, and the reduction of the arteriovenous oxygen differences to 1.01 and 0.71 volumes per cent on the right and left sides, respectively.

§ In C, the results for patient 10 are typical of those obtained for patients 10 to 12, in whom the cortical blood is more equally divided between the right and the left internal jugular vein than it was in the patients listed in A and B. The arteriovenous oxygen differences on the right and on the left side are approximately equal. The control arteriovenous oxygen difference on the right side begins at 9.06 volumes per cent and falls to 7.47, 6.11 and 7.80 volumes per cent during light depression and to 5.84 volumes per cent during deep narcosis. The comparable values for the left side are 8.57, 7.40, 6.20 and 7.05, and 5.89 volumes per cent. In this subject the values obtained during deep anesthesia are not so reduced as were those in our other observations made during profound depression. Probably an accompanying greater fall in blood pressure slowed cerebral blood flow, so that more oxygen was removed from each cubic centimeter of blood passing through the brain.



results obtained with the deeper levels of anesthesia arteriovenous oxygen differences on the two sides were equally diminished. The alterations in blood gases showed that the results were correlated with the degree of anesthesia, so that with the lighter levels of anesthesia the arteriovenous oxygen differences ( $a$ ) were decreased more sig-

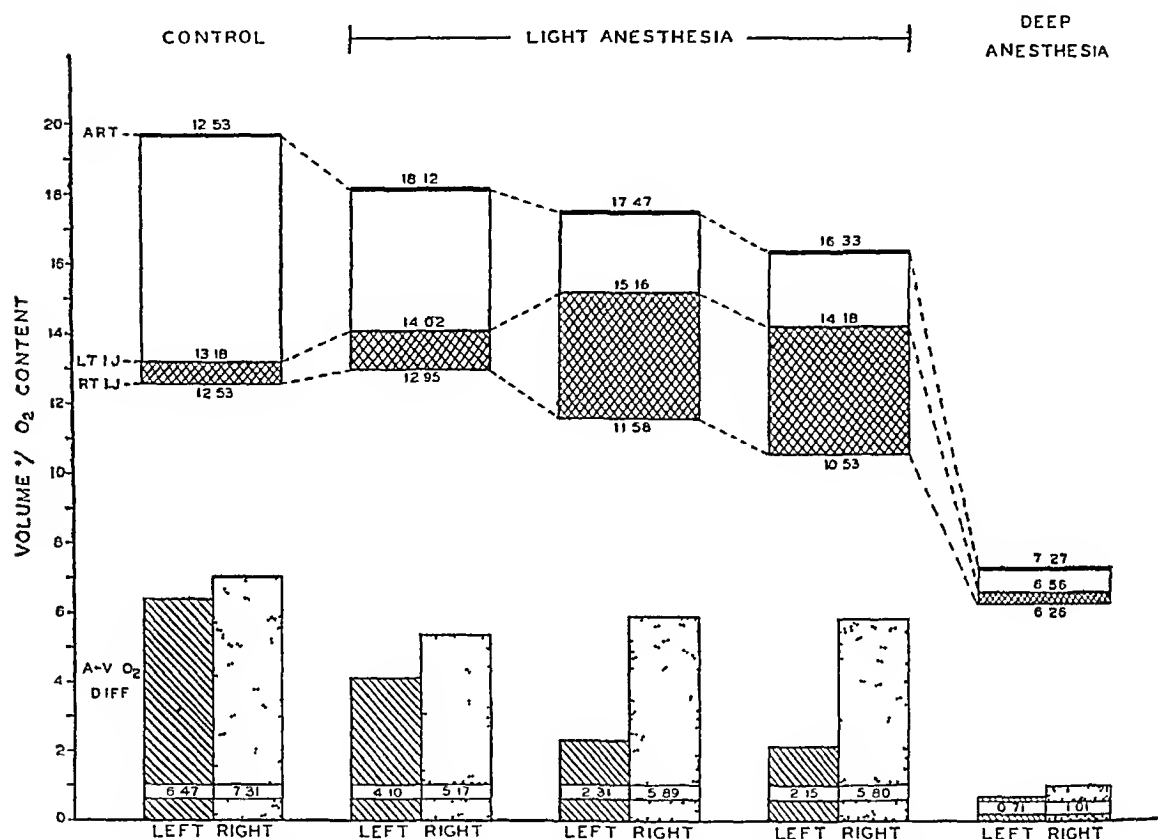


Fig 2—The data for patient 5 are characteristic of the group in which the cortical venous blood is carried chiefly by the left internal jugular vein. During light anesthesia, the arteriovenous oxygen difference on the left side is consistently smaller than that on the right side. During deep depression the arteriovenous oxygen differences are equal on the two sides and within the experimental error. The data are shown in two ways. The arteriovenous oxygen differences for the right and left sides are presented in the columns in the lower part of the figure, and in the upper portion are the values for the oxygen content. The cross hatched area shows the difference between the oxygen content of the right and that of left internal jugular vein. The profound depression of respiration in deep anesthesia is exhibited in the low oxygen content of the arterial blood.

nificantly on the right side than on the left in 4 subjects (table 1 A) and (b) were more reduced on the left side than on the right in 5 subjects (table 1 B). In 3 subjects only did the arteriovenous oxygen differences on the two sides vary only within the experimental error (table 1 C).

It must be emphasized that repeated observations yielded consistent patterns, i e, if in the lighter stages of anesthesia the arteriovenous oxygen difference was smaller on the right side than on the left in the first observation it was smaller in all the succeeding ones. A typical result is that for patient 1 (fig 1), whose right arteriovenous oxygen difference was smaller on the right side than on the left in each experiment made with administration of sufficient pentothal to secure light

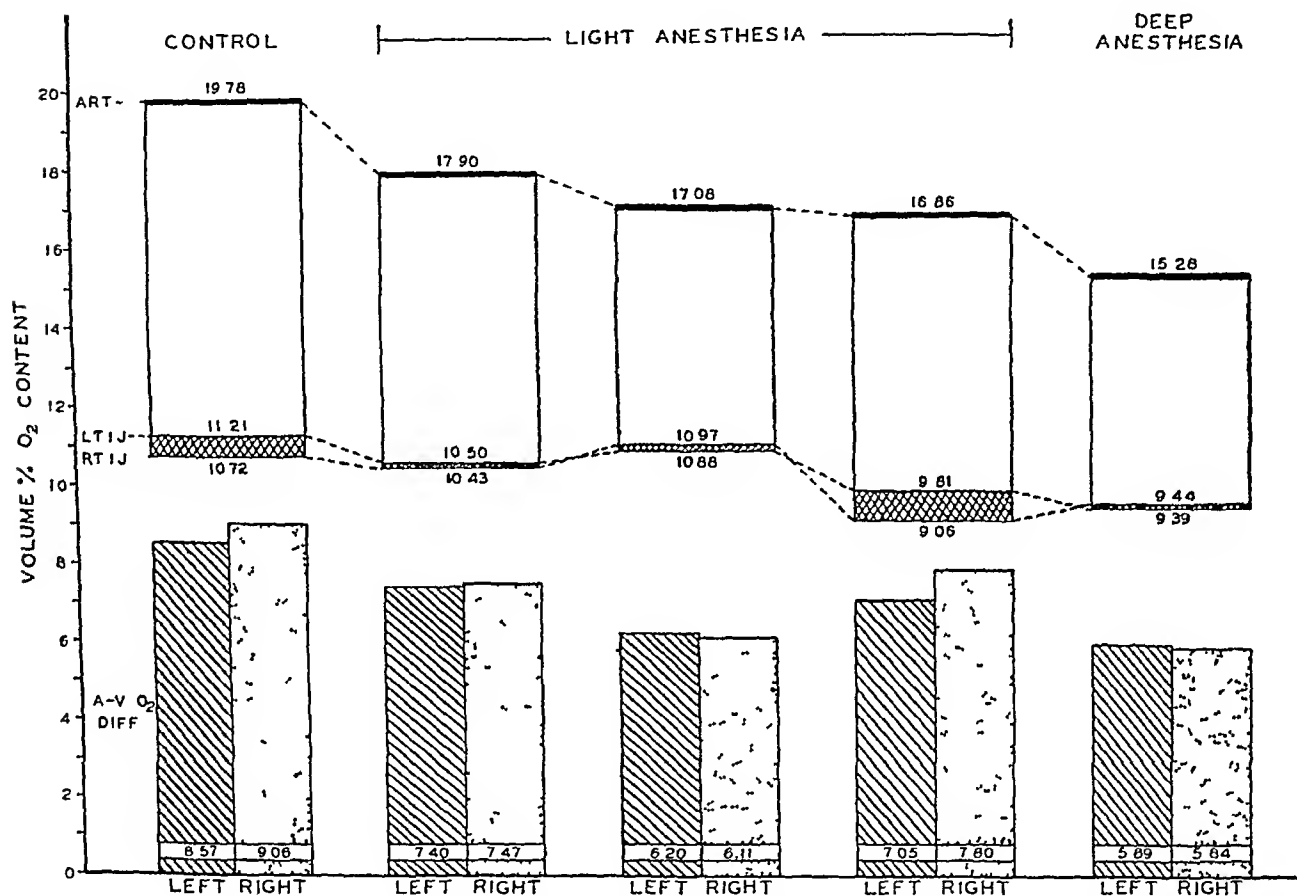


Fig 3—In patient 10 either a torcular Herophili was present or the branches of the superior longitudinal sinus divided its blood approximately equally between the two lateral sinuses. These data are presented twice, once in the lower columns, showing the paired values of the arteriovenous oxygen differences for the two sides, all of which vary within the error of the method, and, again, in the upper portion of the figure, with the values for oxygen content. The cross hatched portion shows the differences between the oxygen contents of the blood of the right and of the left internal jugular vein, none of which, however are significant. The comparatively large arteriovenous oxygen difference found during anesthesia is associated with a profound fall in blood pressure.

depression. Again, for patient 5 (fig 2) the arteriovenous oxygen difference was smaller on the left side than on the right and remained so throughout light narcosis. In deep pentothal anesthesia, however, both patients exhibited arteriovenous oxygen differences which were equal and within the experimental error on the two sides, irrespective of the pattern displayed when the patient was lightly anesthetized. For patient 10 (fig 3) the variations in the arteriovenous oxygen differ-

ences on the right and the left side were insignificant not only in deep anesthesia but also in light depression. This equality between the right and the left side is indicative either of the presence of a torcular or of a division in the blood of the superior longitudinal sinus between the two lateral sinuses.

*Glucose and Lactate*—For the 3 patients for whom values are presented in table 1 C the oxygen contents of the right and of the left internal jugular vein were similar and within the experimental error.

TABLE 2—*Glucose and Lactic Acid Contents of Arterial Blood and of Blood of the Right and the Left Internal Jugular Vein*

Patient	Condition *	Arterial Blood, Mg per 100 Cc		Blood of Right Internal Jugular Vein, Mg per 100 Cc		Blood of Left Internal Jugular Vein, Mg per 100 Cc	
		Glucose	Lactic Acid	Glucose	Lactic Acid	Glucose	Lactic Acid
		A Patients (Table 1C) in Whom Cerebral Venous Return Was About Equal on the Two Sides †					
10	Control			124	11 63	122	11 75
	Light	88	6 28	77	8 49	77	8 26
	Deep	84		81		81	
11	Control	79	9 07	72	10 93	72	10 59
	Light	93	9 07	93	9 30	81	10 00
	Deep	101	12 10	97	8 35	97	8 35
12	Control			77	11 75	77	11 16
	Light	81	8 84	65	7 91	66	6 98
	Deep	77	9 19	74	5 82	74	5 47
	Deep + oxygen	77	5 47	77	9 07	77	6 40
B Patients (Table 1A and B) with Predominant Component of Cerebral Venous Return in Either Right or Left Internal Jugular Vein ‡							
2	Control	86	10 23	68	21 16	68	13 02
	Light	102	8 02	92	7 68	95	7 01
	Light	77	6 05	75	5 93	68	6 74
	Deep	101	10 93	93	7 79	99	6 98
6	Control	103	6 16	99	8 72	99	
	Light	101	12 33	93	7 21	95	8 61
	Deep	97	8 49	90	8 49	95	7 79
	Deep	95	8 26	92	8 96	90	8 72
	Deep	92	6 40	90	6 12	90	6 51
	Deep	138	16 28	131	15 82	127	18 14
7	Control	95	7 44	88	11 16	88	13 49
	Light	99	12 44	88	9 88	92	9 19
	Light	95	11 63	88	11 05	92	7 09

\* 'Light' and 'deep' indicate levels of anesthesia.

† The close agreement between the values for glucose and lactic acid contents of the blood in the right and the left internal jugular vein is apparent.

‡ The values for the glucose and lactate contents of the blood in the right and the left internal jugular vein are in less close agreement than are the comparable values in A.

The glucose and lactate contents of the two internal jugular veins of these 3 patients (table 2 A) displayed the same good agreement except for 1 observation each for glucose and lactate. For the other patients (table 1 A and B) a dissimilarity was noted between the oxygen content of blood of the right and that of the left internal jugular vein, especially during light anesthesia. The data on glucose and lactate for 3 patients of this group are presented in table 2 B. The agreement between the contents for the right and for the left internal jugular vein is not so close in most instances as it is in table 2 A.

When arteriovenous glucose differences for the two sides were considered together, irrespective of the source of the blood, it was found that in 11 resting patients the brain absorbed from 0 to 22 mg from each hundred cubic centimeters of blood passing through that organ. The average arteriovenous glucose difference for 7 of the subjects on whom we had complete data was 9.1 mg per hundred cubic centimeters in the resting condition. After the injection of pentothal sodium an average difference of 7.2 mg per hundred cubic centimeters was obtained during light anesthesia for these same subjects, in deep depression the average fell to 5.4 mg per hundred cubic centimeters. Thus, the gradual decrease in the arteriovenous glucose difference was similar to that observed with oxygen.

#### COMMENT

In order to disclose the effect of light pentothal anesthesia on the cerebral arteriovenous oxygen differences of blood containing the cortical component, whether coming from the right or from the left side, the data in A and B of table 1 were subjected to further analysis. It was found that the control values in these two tables averaged 6.89 volumes per cent, which are in close agreement with previous observations.<sup>4c</sup> With light anesthesia the average for the arteriovenous oxygen difference of blood carrying the cortical component was 2.75 volumes per cent, and the average for the arteriovenous oxygen difference from the opposite side was much greater, 5.9 volumes per cent. For deep anesthesia an average of 2.03 volumes per cent was observed, provided the results accompanied with a great decline of blood pressure were omitted from the calculations, but if they were included the average was raised somewhat, to 2.93 volumes per cent.

The decrease in the arteriovenous oxygen difference produced by pentothal sodium confirms the observations in previous experiments with amytal, in which, however, the amount of the drug was sufficient only to place the subject in light depression. Dameshek, Myerson and Loman<sup>9</sup> reported that the average arteriovenous oxygen difference of 6.4 volumes per cent fell to 5.7 volumes per cent after the administration of sodium amytal. Confirming this small, but significant, decrease are the unpublished results of Dr F. A. Hale and one of us (H. E. H.), who found an average arteriovenous oxygen difference of 5.8 volumes per cent after the intravenous administration of sodium amytal. This value is lower than the average arteriovenous oxygen difference for normal man 6.7 volumes per cent.<sup>10</sup> These decreases in arteriovenous

9 Dameshek, W., Myerson, A., and Loman, J. The Effects of Sodium Amytal on the Metabolism, *Am J Psychiat* **91** 113-135, 1934.

10 Himwich, H. E., and Fazekas, J. F. Cerebral Arteriovenous Oxygen Difference, *Arch Neurol & Psychiat* **50** 546-551 (Nov) 1943.

oxygen difference were less pronounced than those reported in the present investigation, chiefly because in the previous work consideration was not given to the anatomic arrangement in the cerebral venous return or to the resulting discrepancies between the arteriovenous oxygen differences on the two sides during light anesthesia. All results were, therefore, averaged instead of presenting the effect on the cerebral component separately.

Schmidt, Kety and Pennes<sup>11</sup> reported that pentothal produced no consistent change in the cerebral arteriovenous oxygen difference in the monkey. If the discrepancy between the results obtained in the monkey and in man is not due to a species difference, three other reasons, based on the difference in experimental conditions, may be suggested. First, the control values of Schmidt and co-workers were made during light barbiturate anesthesia, and the present observations disclosed that under this condition the cortical component is depressed. Second, the blood of the right and of the left internal jugular vein were mixed in a common tube before the collection of the blood. To understand how this mixture cloaks the effect of pentothal on the cortical component, it is necessary to analyze the results for the patients (table 1 C) in whom both internal jugular veins carried the same kind of blood, because in these men the samples of blood were identical as the mixture of the blood took place within the cranial cavity. The average for the controls (table 1 C) was 7.62 volumes per cent. The average for patients under light anesthesia was 6.81 volumes per cent, a difference which is not significant. Thus, a mixture of the blood of the two internal jugular veins may explain, in part, the failure of the arteriovenous oxygen differences to decrease in the experiment on the monkeys. Finally, the average for the observations made on patients in deep anesthesia was 2.47 volumes per cent when the blood pressure was relatively consistent, but the value rose to 5.87 volumes per cent for those experiments in which the blood pressure began to fail. Thus, it is possible that the results of Schmidt and co-workers, which were obtained from monkeys in deepest anesthesia, revealed this type of secondary increase.

In our experiments, there may have been two causes for the greater depression of arteriovenous oxygen difference on one side. Either the blood passes through the cerebral hemispheres faster than in the lower parts of the brain, or the metabolism of the cerebral cortex is depressed more than that of the subcortex. Though we do not possess data on the effect of pentothal sodium on the cerebral blood flow of our patients,

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11 Schmidt, C. F., Kety, S. S., and Pennes, H. H. Gaseous Metabolism of the Brain of the Monkey, *Am J Physiol* **143** 33-52, 1945

we know that in the monkey<sup>11</sup> and in the dog<sup>12</sup> pentothal sodium diminishes the volume of blood passing through the brain. It is also probable that the cerebral blood flow of our patients was diminished, for the systolic pressure fell from 5 to 50 mm below the control values during our observations on the various patients, and a lowered blood pressure curbs cerebral flow. It would not seem likely, therefore, that the blood flow is accelerated in the cerebral hemispheres. If the cerebral blood flow is slowed, then a fall in the arteriovenous oxygen difference indicates a depression of cerebral oxidation. To obtain a final answer, it is necessary to determine the effect of pentothal sodium on blood flow through each internal jugular vein, and this will be our next task.<sup>13</sup>

These results yield a functional corroboration for the anatomic observation<sup>4a,b</sup> of an asymmetric venous return from the cerebral hemispheres and from the basal ganglia for 9 of 12 patients. The relatively large percentage of subjects, 25 per cent, with an approximately equal distribution of cortical blood in the two internal jugular veins may be ascribed in part to the sampling of a small, and hence not representative, number of patients. It must also be remembered that there are two ways in which the blood of the superior longitudinal sinus may appear in both internal jugular veins. One is comparatively rare, through a torcular Herophili, in the other the branches of the superior longitudinal sinus divide its blood approximately equally between the right and the left lateral sinus.

All the data presented indicate that in the lighter stages of anesthesia the oxidations in the cerebral hemispheres are more depressed than those of the other portions of the brain and that this depression is a progressively descending phenomenon which may finally involve the entire organ. The persistent effect on the cerebral hemispheres is in accordance with the well known decorticating action of the barbiturates. But that the metabolic retardation is not limited to the cortex is shown by the impairment of the arterial oxygen, which becomes especially pronounced when depression of the medulla oblongata takes place during deep anesthesia. Then anoxic anoxia is superimposed on the histotoxic

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12 Homburger, E. G., Himwich, W. A., Maresca, R., and Himwich, H. E. Effect of Pentothal Anesthesia on Canine Cerebral Cortex, *Am. J. Physiol.*, to be published.

13 Since this investigation was submitted for publication, we have been able to show that during pentothal anesthesia cerebral blood flow is slowed and that the slowing is greater in the cerebral hemispheres than in the lower portions of the brain. It was further demonstrated that cerebral metabolic rate was diminished during pentothal narcosis and that the diminution exhibited a definite pattern, the cortical oxidations being depressed earlier and more profoundly than those of the rest of the brain (Himwich, W. A., Homburger, E., Maresca, R., and Himwich, H. E. Brain Metabolism in Unanesthetized and Anesthetized Man, *Federation Proc.* 5:47, 1946).

anoxic action of the barbiturate, as the function of the respiratory center is impaired because of its metabolic depression. This type of medullary depression does not include temporary inhibition of the respiratory center, which can occur at any time in the course of pentothal anesthesia if the rate of intravenous injection is rapid.

When respiratory inhibition occurs during the lighter stages of anesthesia, it is not directly referable to depression of medullary oxidations but may be regarded as a specific effect on the respiratory center, and in the lighter stages it is transitory. Tidal exchange becomes progressively diminished with deepening anesthesia, and this phenomenon is the result of the withdrawal of metabolic support. The consistent diminution in the arterial oxygen content demonstrates the progressive inhibition of medullary oxidations. Thus, a distinction must be drawn between the two effects of barbiturate on the nerve tissue: (1) a direct, specific depression exerted particularly on visceral nuclei, an action which is not necessarily proportional to the metabolic depression, and (2) the withdrawal of the metabolic support necessary to maintain nerve function.

In terms of blood gases, an inequality in arteriovenous oxygen differences between the right and the left side indicates in most patients that the cerebral hemispheres are depressed more than other parts of the brain, a condition designated in the present report as light anesthesia. When not only the cerebral hemispheres but the basal ganglia are included in the depression, deep anesthesia is observed as the arteriovenous oxygen differences become equal, within the experimental error, on the two sides. This deep depression may be progressive and proceed through the midbrain to the medulla oblongata.

#### SUMMARY AND CONCLUSION

In this investigation on the pattern of the action of pentothal sodium on the brain it was possible to show that the cerebral hemispheres are the areas first involved in the depressant action of this drug, because of the peculiarities of the anatomic venous cerebral return, which in the majority of patients directs most of the blood from the cerebral hemispheres either to the right or to the left internal jugular vein and a major portion of the blood from the basal ganglia to the opposite vein. A total of 36 observations were made on 12 subjects under pentothal anesthesia. Of 22 observations, made at the lighter levels of anesthesia, the results may be divided into two groups. In 9 of the subjects the arteriovenous difference on one side was more depressed than that on the opposite side, and in the 3 remaining patients the arteriovenous differences were similar on the two sides. Further evidence supporting the differences between the values for the right and the left internal jugular vein is obtained from the data for glucose and lactate, for in the same 3 patients

in which the arteriovenous oxygen differences were always within the experimental error the arteriovenous glucose and arteriovenous lactate differences exhibited a similar agreement, while in the other 9 patients the paired results did not show a similar precise concordance. With deeper anesthesia the subcortical parts became more involved, and the paired arteriovenous oxygen differences for the two sides were greatly depressed and within the experimental error in all but 2 of 14 observations. These results indicate that oxidation is not decreased to the same extent in all parts of the brain at the lighter levels of barbiturate anesthesia but that the cerebral hemispheres are the areas of the brain preponderantly involved in the depressant action of the drug. The other parts of the brain gradually suffer an increasing inhibition of oxidation as the deep levels of pentothal anesthesia are produced.

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# EFFECTS OF ANTIBIOTIC SUBSTANCES ON THE CENTRAL NERVOUS SYSTEM

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AND

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THERE HAS been a singular dearth of experimental studies on the effects of penicillin and other antibiotic substances on the physiologic processes of the nervous system. The lack of clinical evidence of neural toxicity when penicillin is administered systemically or intrathecally is astonishing when the antibacterial potency of the drug is considered. However, the observation of convulsive manifestations following intraventricular administration<sup>1</sup> led to a study of the effects of antibiotic substances on the nervous system. This report concerns the neuropharmacodynamics of penicillin,<sup>1</sup> streptomycin, clavacin, actinomycin and streptothricin. An attempt was made to test the effects of aspergillic acid on the brain, but its relative insolubility in water made the experiment unsatisfactory.

## PENICILLIN <sup>2</sup>

Penicillin, one of the antibiotic principles obtained from *Penicillium notatum*, is the best known and one of the most powerful of the bactericidal substances of microbial origin.

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The work described in this paper was done under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and the University of Chicago.

1 Johnson, H C, and Walker, A E. Intraventricular Penicillin. A Note of Warning, J A M A **127** 217-219 (Jan 27) 1945.

2 The penicillin was provided by the Office of Scientific Research and Development from supplies assigned by the Committee on Medical Research for Experimental Investigations, recommended by the Committee on Chemotherapeutics and Other Agents of the National Research Council.

Dr D F Robertson, of Merck & Co, Inc, supplied the streptothricin, Dr G W Rake, of the Squibb Institute for Medical Research, the aspergillic acid, Dr G M Everett, of Abbott Laboratories, the streptomycin and clavacin, and Dr S A Waksman, State of New Jersey Agricultural Experimental Station, the actinomycin.

When administered systemically it apparently does not reach the central nervous system in appreciable amounts. However, there is evidence that in the presence of meningeal irritation the penicillin may pass into the spinal fluid in increased amounts and may reach concentrations sufficiently high to kill the more sensitive bacteria. There appears to be little clinical evidence, however, that penicillin given systemically induces alteration in nervous function. In view of the fact that convulsive manifestations were noted when penicillin was applied to the cerebral cortex,<sup>3</sup> electroencephalographic studies were made on a series of 51 patients who were receiving penicillin therapy for some condition other than a primary neurologic one. The records of only 20 patients were normal at all times, the other 31 patients showed abnormalities on one or more examinations. Control records taken before and after penicillin therapy were available for 18 of these 31 patients. In 4 patients having control records before and after the therapy, there was evidence of increased electrical activity during the administration of the drug, with normal records both before and after the therapy. On two occasions during the course of penicillin therapy, 1 of these patients showed evidence in the electroencephalogram of abortive or subclinical epileptic "seizures" which were not seen in any of the control records. Seven patients showing increased activity in the electroencephalogram during the period of penicillin therapy had a similar pattern after the withdrawal of therapy. Unfortunately, pretreatment records were not made. Six of these 7 patients were children between 5 and 14 years of age, their records suggested a convulsive diathesis. Four patients with control records only after therapy showed pronounced diminution of electrical activity after withdrawal of the drug. For 2 patients the electrical activity of the brain was less during administration of the drug than in the control records. On the basis of these observations it appears that subclinical alterations in cerebral function may occur during the time of administration of penicillin in somewhat more than 50 per cent of cases (figs 1, 2, 3 and 4).

Although usually only subclinical effects are present during systemic administration, overt clinical manifestations may develop when the drug is applied directly to the central nervous system, either by intrathecal injection or by direct application to the brain. After lumbar intrathecal injection the mild meningeal irritation, manifested by pleocytosis and increased protein in the spinal fluid, is well known. That neural complications may develop is not so well recognized. In the monkey the lumbar injection of 20 000 units of penicillin causes

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3 Walker, A. E., and Johnson, H. C. Convulsive Factor in Commercial Penicillin, *Arch Surg* 50:69-73 (Feb) 1945

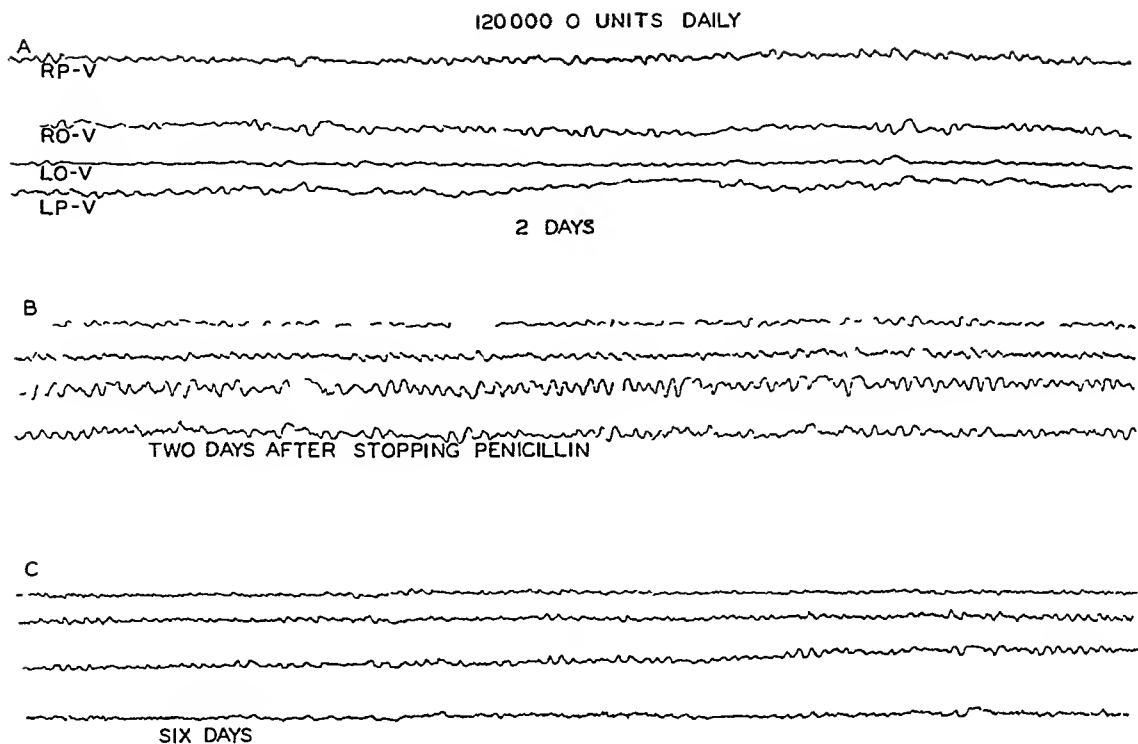


Fig 1—Electroencephalograms of a woman aged 19 who had a wound infection following thoracolumbar sympathectomy for high blood pressure

(A) The record shows considerable abnormal activity two days after penicillin therapy was started (B) Fifteen days later, or two days after stopping penicillin, the record shows substantial increase of abnormal activity in all areas. Much of it appears as a slowed alpha wave (about 7 cycles per second) but there is considerable energy of both faster and slower frequency than the alpha activity (C) A tracing taken six days after penicillin treatment was stopped shows substantial decrease of abnormal activity.

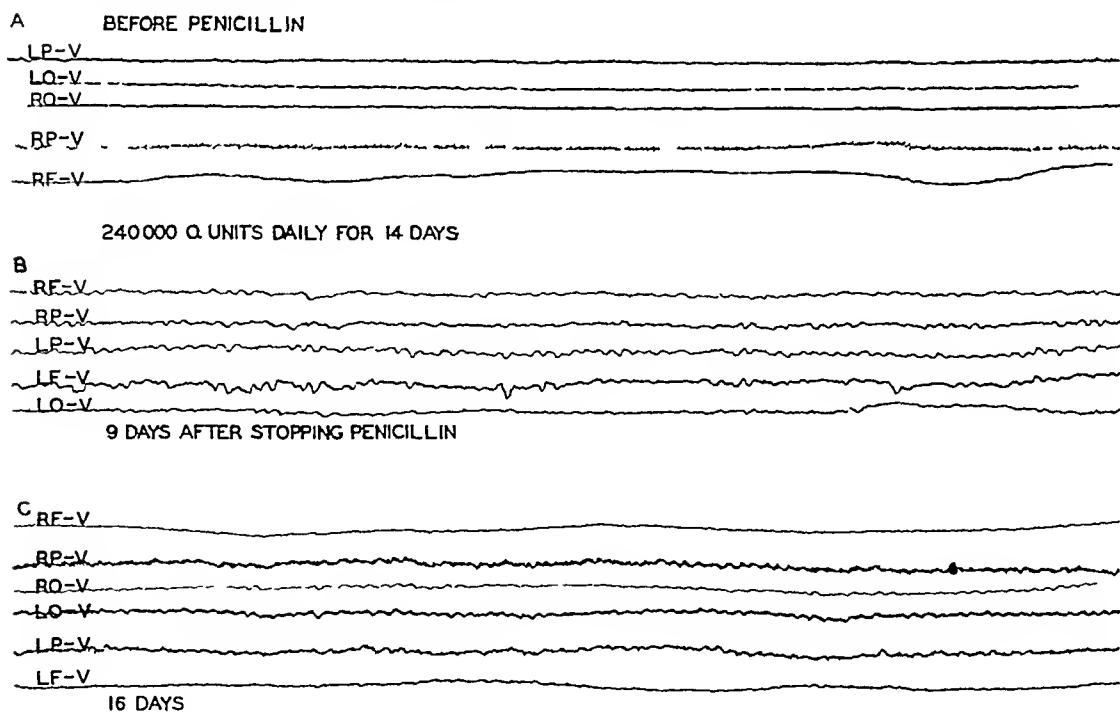


Fig 2—Electroencephalograms of a woman aged 36 with an actinomycotic infection of the chest and spine

A, a tracing taken before penicillin therapy was started, shows only a little muscular activity in the right parietal lead. B is a record taken nine days after administration of penicillin for fourteen days, C is a tracing taken sixteen days after penicillin therapy was stopped.

100000 O UNITS DAILY

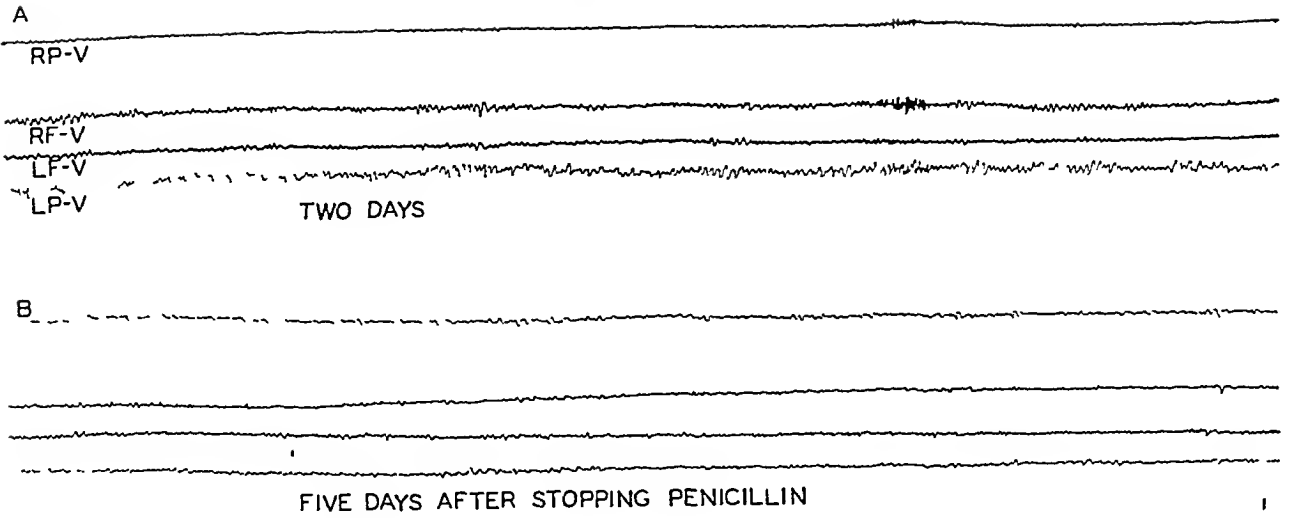


Fig 3—Electroencephalogram of a woman aged 35 with an infection of the urinary tract *A*, a record taken two days after penicillin therapy was started, shows considerable fast, beta-like activity, which at times is sharp and spiky *B*, a record taken five days after penicillin therapy was stopped, shows substantial decrease in the fast activity

120000 O UNITS DAILY

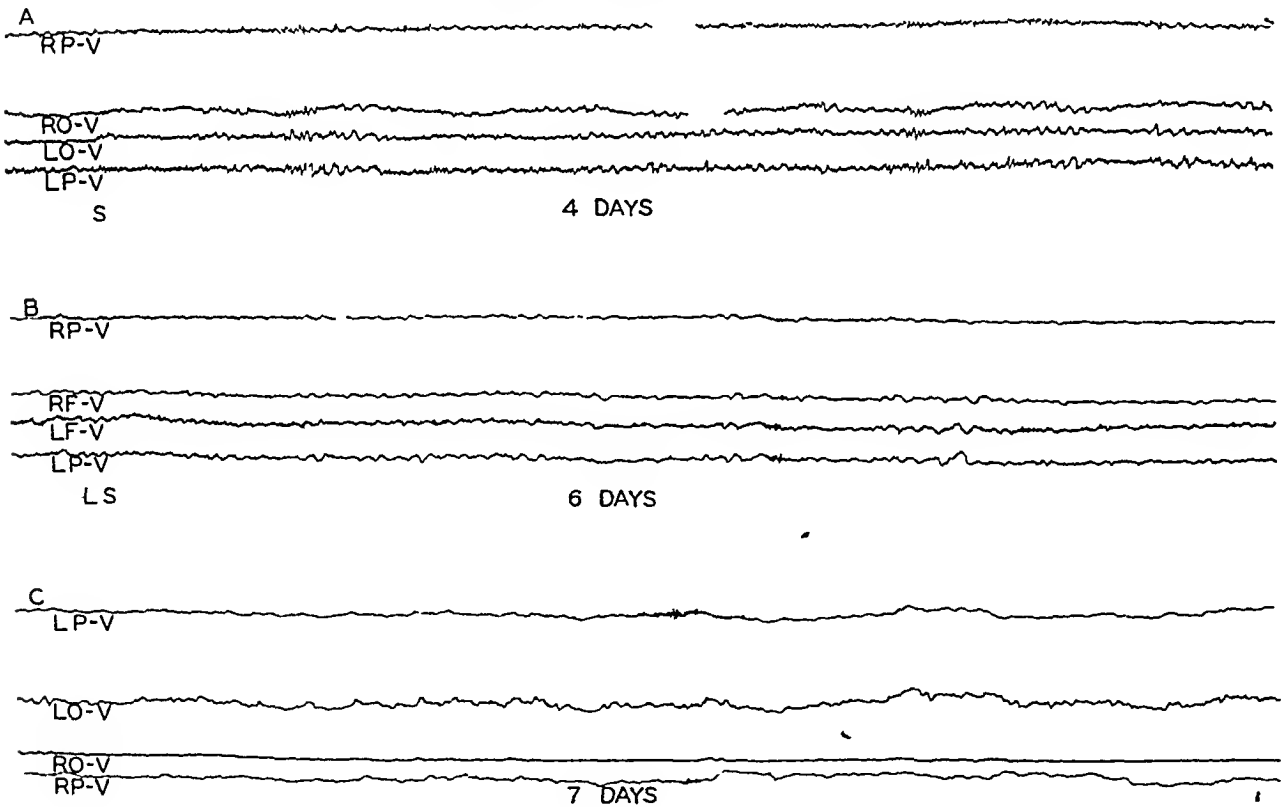


Fig 4—*A*, electroencephalogram of a man aged 38 who had an infection of the urinary tract after removal of a stone from the renal pelvis. The record, taken four days after penicillin therapy was started shows fast activity in all leads

*B*, record of a woman aged 24 who had an abscess in a laparotomy wound, taken six days after treatment with penicillin was started. Another record, taken three months after penicillin therapy was stopped, did not look very different. The patient was thought probably to have an epileptic diathesis.

*C*, electroencephalogram of a 9 year old girl who broke her arm six days before penicillin therapy was started. The record was taken seven days after administration of penicillin was begun. The irregularities were considered questionably epileptic.

the animal to inspect, rub and then vigorously scratch his tail and perianal region for a half-hour or more after the injection. After a few hours the animal appears normal again. In man, however, a number of cases of sacral radiculitis have been reported to follow intrathecal penicillin therapy<sup>4</sup>. Paresthesias, urinary retention and sensory and motor disturbances in the lower extremities have characterized the clinical picture. Fortunately, the radiculitis has usually cleared up in a few weeks or months.

Probably because the diffusion of penicillin from the lumbar subarachnoid space is slow, alterations in cerebral function have not been seen even after the injection of enormous amounts of penicillin by

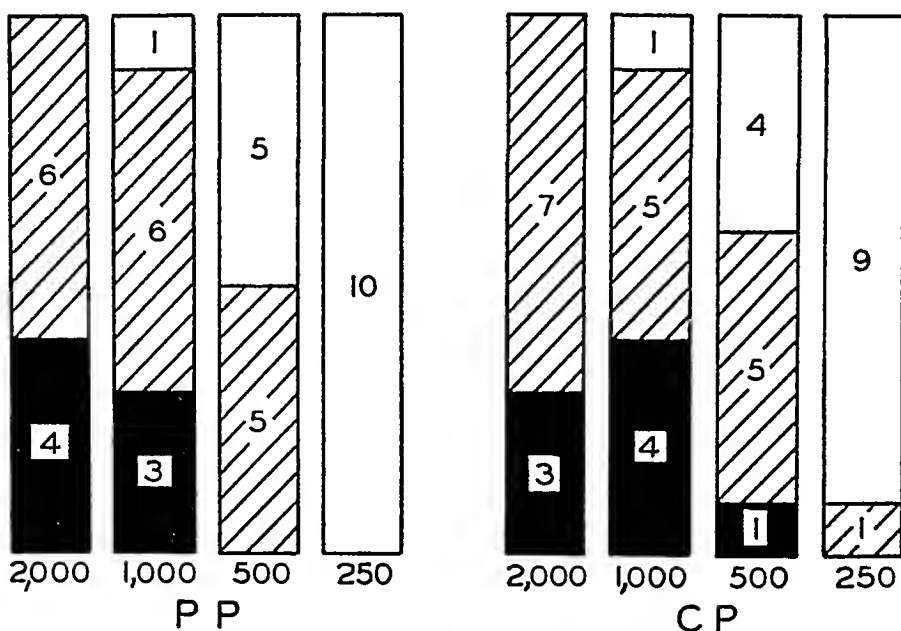


Fig 5—Histograms showing the convulsive responses (generalized fits, solid black, unilateral twitching, lined, and no convulsive manifestation, white) to the intracortical injection of crystalline (P P) and commercial (C P) penicillin in doses of from 250 to 2,000 Oxford units

lumbar puncture. However, if large doses of the drug are introduced into the cisterna magna, serious sequelae may result. In both the experimental animal and man convulsive seizures, coma, and even death, may occur. In the monkey 10,000 units of penicillin may induce these complications, in man 40,000 units has been known to produce them<sup>5</sup>. In

4 Sweet, L. K., Dumoff-Stanley, E., Dowling, H. F., and Lepper, M. H. The Treatment of Pneumococcal Meningitis with Penicillin, *J. A. M. A.* **127** 263-267 (Feb. 3) 1945

5 Neyman, C. A., Heilbrunn, G., and Youmans, G. P. Experiments in the Treatment of Dementia Paralytica with Penicillin, *J. A. M. A.* **128** 433-434 (June 9) 1945

experimental animals the minimal convulsive dose of penicillin has been determined. In the dog and monkey approximately 500 Oxford units of penicillin applied to the cerebral cortex is sufficient to induce convulsive manifestations, which initially consist of clonic spasms of the

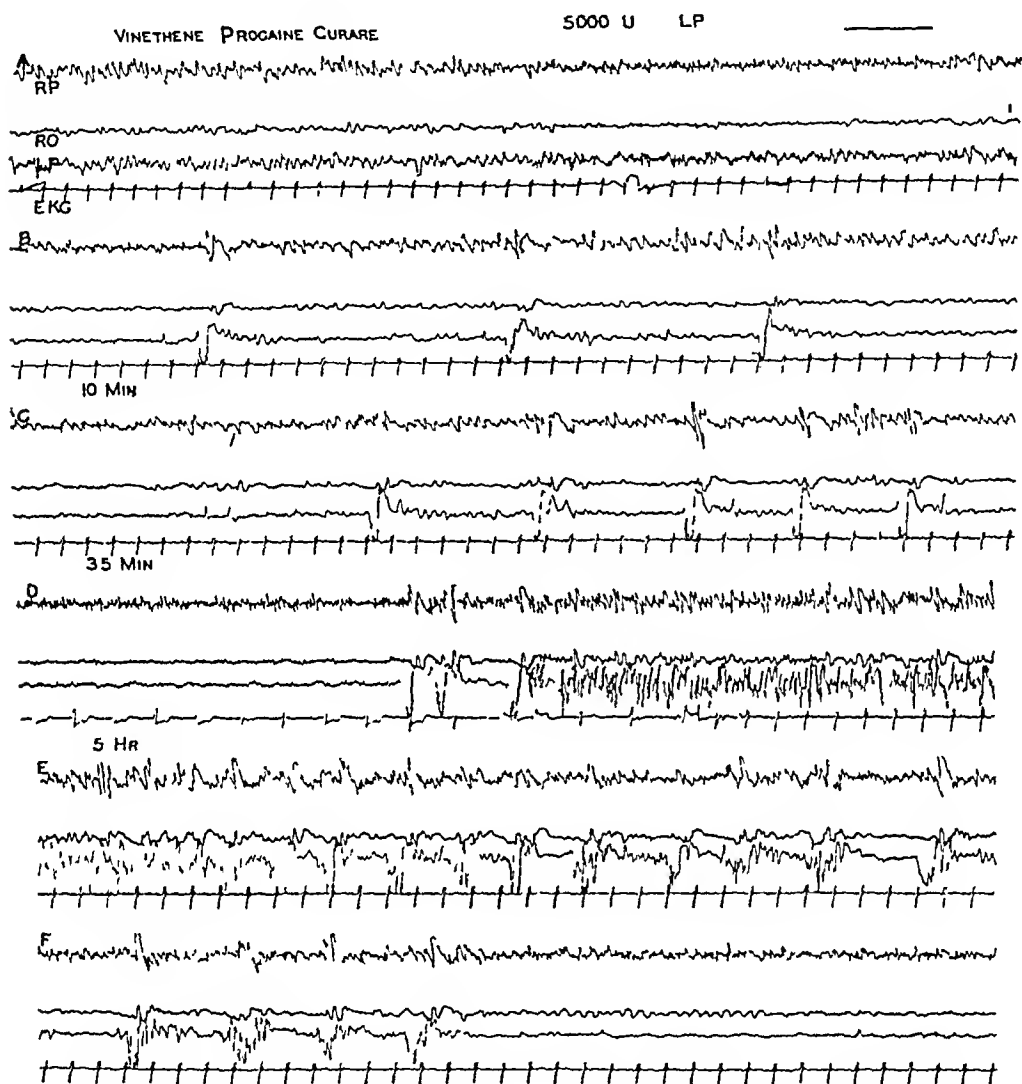


Fig 6—Electrocorticograms taken from electrodes screwed into the calvaria of a cat prepared with vinethene anesthesia. The scalp was procainized, and the animal was given curare and artificially aerated.

A, control record. *R P* indicates the right frontoparietal lead, *R O*, the right parieto-occipital lead, *L P* the left frontoparietal lead, and *EKG* the electrocardiogram.

B, record taken ten minutes after an injection of 5,000 Oxford units of penicillin in the subdural space of the left parietal region. The spikes are particularly prominent in the left frontoparietal lead.

C, record taken thirty-five minutes after the injection, showing the spikes more frequent and larger in the right-sided leads.

D, E and F, records taken five hours after the injection. These records are continuous, showing the electroencephalographic manifestations of a generalized convulsion.

An interval of one second is indicated by the horizontal line in the upper right corner, just below the first tracing at the right side. A calibration of 60 microvolts.

contralateral extremities but later usually involve all limbs in the manner of a generalized epileptic seizure. In man, the convulsive threshold, as determined by as yet inadequate studies, appears to be considerably higher. These toxic manifestations are not due to impurities in the penicillin, for pure crystalline penicillin induces the attacks (fig 5). In the experimental animal, monkey, cat or dog, the convulsive phenomena usually spontaneously decrease and disappear in eight to ten hours. Occasionally the animal passes into coma and dies. Anticonvulsant medication, such as administration of phenobarbital, will control the attacks in experimental animals. After the spontaneous or pharmaceutically induced cessation of the seizures, the animal quickly recovers and the next day appears normal. Gross examination of the brains of animals so treated shows only a small area of brownish discoloration at the site of the injection. Microscopic studies of these lesions reveals a small granuloma, with lymphocytic infiltration practically confined to the area of the injection.

It may, then, be concluded that penicillin when applied to the central nervous system in adequate amounts (fortunately, far above therapeutic requirements) will induce convulsive manifestations, which usually are of a temporary nature. These clinical fits are accompanied with the electroencephalographic manifestations which characterize epileptic attacks (fig 6).

#### STREPTOMYCIN

Streptomycin, a bactericidal substance obtained from *Actinomyces griseus*, is the least toxic of the antibiotic derivatives of the actinomycetes<sup>6</sup>. It is effective against gram-negative bacteria in general, as well as against certain gram-positive organisms.

Knowledge of the effects of streptomycin on the nervous system is based on experimental studies on monkeys and cats. After 10,000 units of streptomycin was injected, without technical difficulty, into the cisterna magna of a monkey, within two minutes the animal became unsteady and so ataxic that standing or sitting was impossible. A spontaneous nystagmus and a fine tremor of the head developed. The ataxia persisted for several hours, but the following morning the animal appeared normal. In another animal the injection of 5,000 units of streptomycin induced the same phenomena. When 2,500 units was injected in another monkey, the animal sat quietly humped up in its cage for several hours. An intracisternal injection of 1,250 units of streptomycin in a monkey caused no apparent abnormality. The

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<sup>6</sup> Waksman, S. A., Horning, E. S., and Spencer, E. L. Two Antagonistic Fungi, *Aspergillus Fumigatus* and *Aspergillus Clavatus*, and Their Antibiotic Substances, *J. Bact.* **45** 233-248 (March) 1943.

injection of 1,250 units of streptomycin in the parietal cortex of each of 10 monkeys induced in 2 animals slow, awkward waving movements of the upper extremity contralateral to the site of injection and slow movement of retraction of the corner of the mouth. These phenomena began approximately one-half hour after injection, lasted for one hour and gradually subsided. When the experiment was repeated on another day, 4 of the 10 monkeys exhibited the peculiar slow movements of the

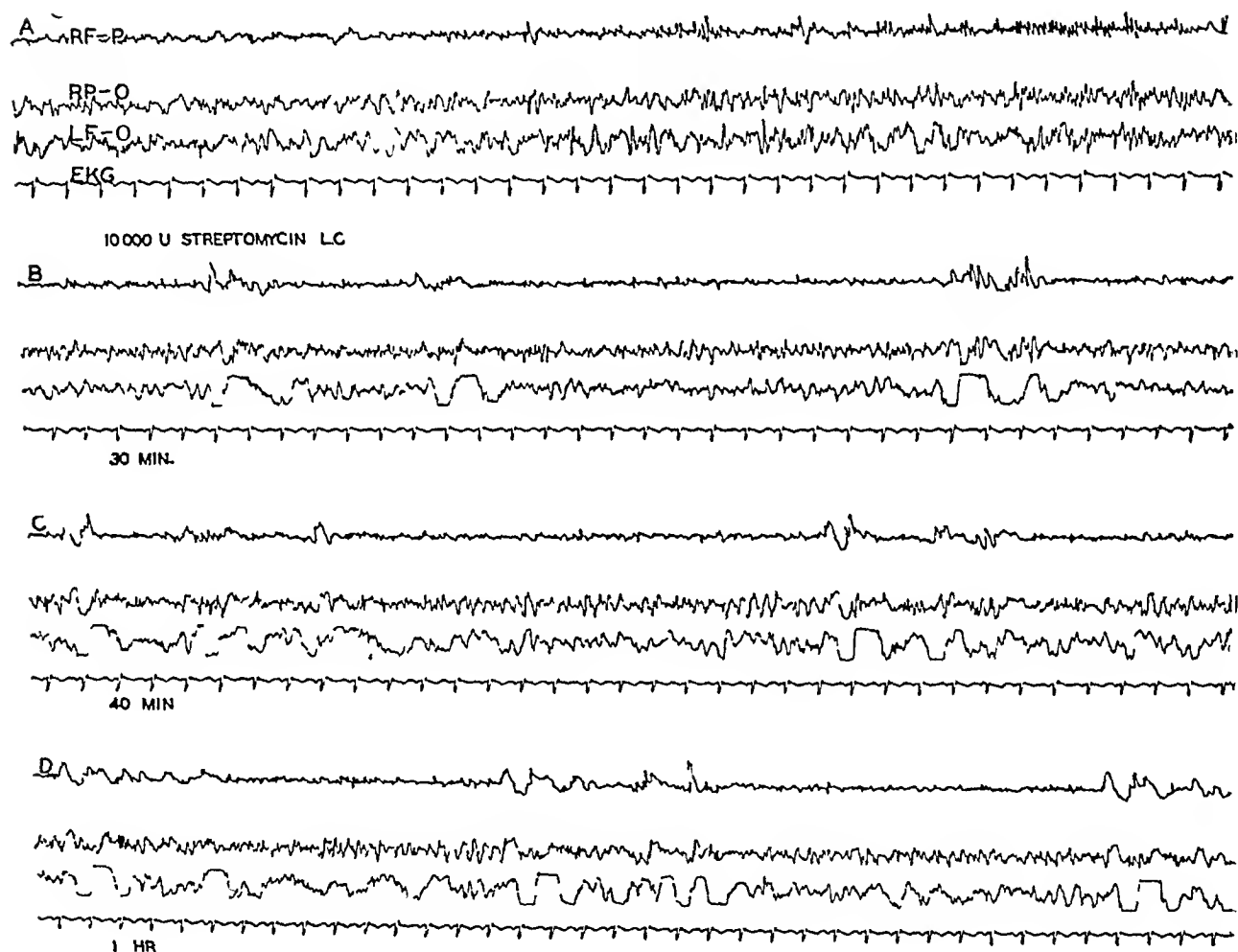


Fig 7—A series of electroencephalograms taken on a monkey prepared with procaine anesthesia, curarized and artificially aerated. The leads were as follows: *RF-P*, right frontal and parietal leads, *LF-O*, left frontal and occipital leads, *EKG*, electrocardiogram taken from needle electrodes in the muscles of the two upper extremities. The animal had had 25,000 units of penicillin implanted in the right frontal area six weeks before this experiment. Probably the spiky, irregular hyperactivity of the cerebral cortex is due to this implant. *A*, control record, *B*, record taken thirty minutes after intracortical injection of 10,000 units of streptomycin into the left central (*LC*) region, showing more pronounced spikes and humps, *C*, record taken forty minutes after injection, with the humps and spikes still apparent, *D*, record one hour after the injection. The irregular activity with spikes and humps, particularly on the left side, is prominent.

The horizontal line at the base indicates an interval of one second, the vertical line at the right, a calibration of 60 microvolts.



contralateral extremities for one to two hours. The following day all the animals appeared normal. Gross examination of the brain of these animals showed the same minor changes as in the brain into which penicillin had been injected. Electroencephalograms taken after the application of 5,000 to 10,000 units of streptomycin to the cerebral cortex of 3 cats and 3 monkeys showed waves or humps, lasting one-half second and occasional spikes from the leads on the side of injection. In some animals, particularly in the monkeys, the cortical activity over the entire brain decreased and remained at a low level for one and a half to three hours (fig 7).

It is concluded that streptomycin applied to the central nervous system will induce mild convulsive manifestations of a temporary nature. The clinical and electroencephalographic manifestations are less severe than those produced by equivalent (at least in terms of units) doses of penicillin.

#### STREPTOTHRICIN

Streptothricin, an antibiotic substance isolated by Waksman and Woodruff<sup>7</sup> from *Actinomyces lavendulae*, has a pronounced bactericidal effect on gram-negative and on some gram-positive bacteria. Unfortunately, the drug is fairly toxic when administered systemically. Its local application to the cerebral cortex of the cat and monkey in doses of 5,000 to 10,000 units induced clinical and electroencephalographic evidence of convulsive phenomena, which persisted for two to three hours and then spontaneously ceased (fig 8).

In 2 monkeys, after intracortical injection of 5,000 units of streptothricin the convulsive phenomena continued to be manifested as twitching of the side of the face and the ipsilateral upper extremity for more than two weeks, at the end of which time the animals were killed. Beneath the site of injection an area of encephalomalacia was present, with numerous petechial hemorrhages. It would appear, then, that streptothricin not only is a convulsive agent but in some cases causes a necrobiotic reaction in the brain.

#### ACTINOMYCIN

Actinomycin, a crystalline substance, isolated by Waksman and Woodruff<sup>7</sup> from *Actinomyces antibioticus*, is a powerful bacteriostatic agent but is highly toxic when given systemically to experimental animals.

The effect of actinomycin on the central nervous system has been studied in 11 monkeys and 2 cats. In 1 monkey 1 mg. of actinomycin

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<sup>7</sup> Waksman, S. A., and Woodruff, H. B. Selective Antibiotic Action of Various Substances of Microbial Origin, *J. Bact.* **44** 373-384 (Sept.) 1942.

(equivalent to about 1 mg of crystalline penicillin) dissolved in isotonic solution of sodium chloride was injected into the cisterna magna. The animal appeared normal until about nine hours later, when it became noisy and restless. If it was disturbed, fascicular twitchings were noted in the muscles of the extremities. Twenty-two hours after the injection the animal was noisier, appeared apprehensive and was lying down in the cage. The fasciculations of the limb musculature were more violent, and local and generalized tonic spasms developed. Twenty-eight hours after the injection the animal died. The brain appeared grossly normal,

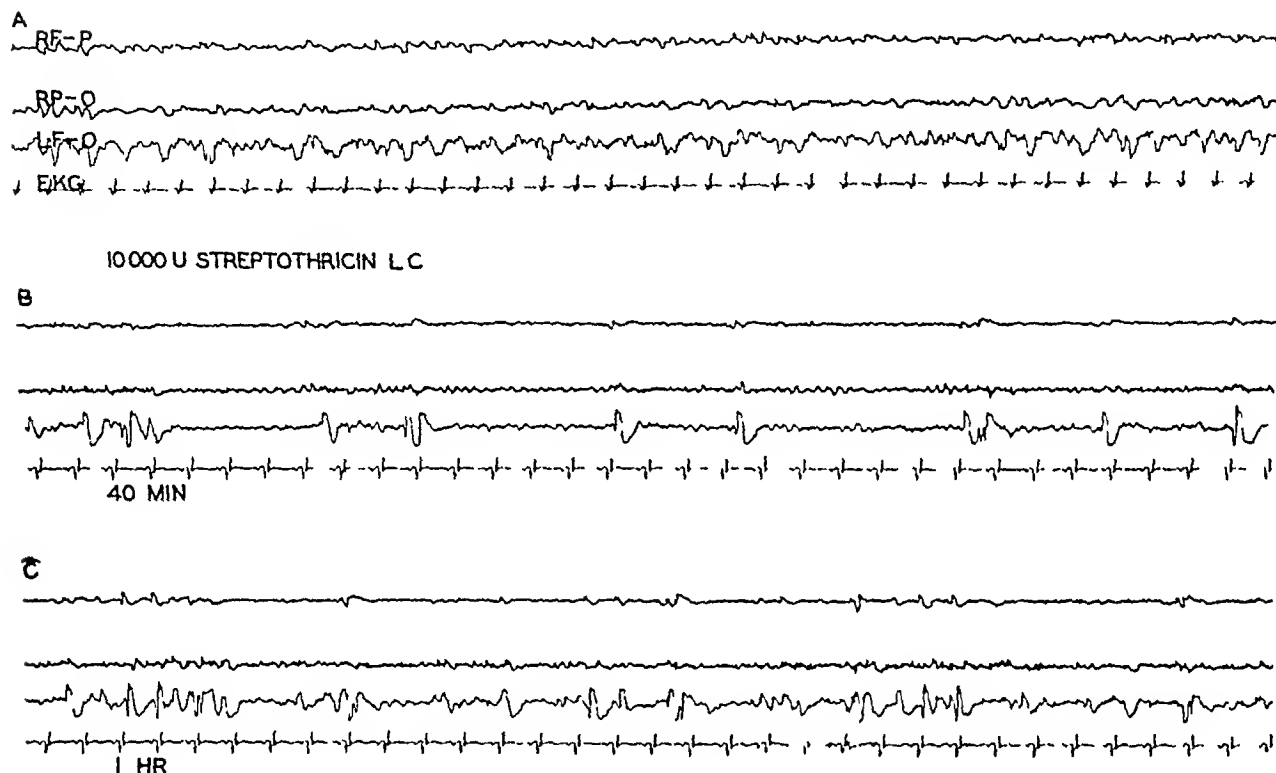


Fig 8—Electroencephalograms of a cat prepared with procaine anesthesia, curarized and artificially aerated. The leads are as follows *RF-P*, right frontal and parietal leads, *RP-O*, right parietal and occipital leads, *LF-O*, left frontal and occipital leads, *EKG*, electrocardiogram taken from needle electrodes in the muscles of the two upper extremities.

*A* control record, *B*, record taken forty minutes after injection of 10,000 units of streptothricin in the left central region (*LC*), showing the generalized decreased cortical activity and spikes, which are more pronounced on the left side than on the right, *C*, record one hour after the injection. The cortical activity is returning, but the spikes are still present.

The horizontal line at the base represents an interval of one second, the vertical line at the right, a calibration of 60 microvolts.

but histologic examination showed a severe meningitis, with leukocytic infiltration and neuronal changes in the cerebral cortex and brain stem.

In a series of 10 monkeys, 1 mg of actinomycin was injected into the left parietal region of the cerebral cortex. The animals appeared well on the day of injection, but the next day all were apathetic, akinetic

and anorexic. On the second day spasms of the forelimbs were noted in several animals. On the morning of the third day 3 of the animals were dead. The others were prostrated, 6 of them had right-sided clonic fits, lasting two to three minutes and occasionally developing into generalized convulsions. One of the 6 animals had right hemiplegia. Three of these animals were killed. Of the 4 remaining monkeys, 1 died on the fifth day, 1 on the sixth day and 1 on the seventh day, and the last animal was killed on that day. The brains of all ten animals presented similar lesions. The left cerebral hemisphere was swollen, and about the point of injection was a discolored area, varying from a few millimeters to 2 or 3 cm in diameter. Sections of the brain showed an area of necrosis below the point of injection, with pronounced edema and perivascular hemorrhages in the surrounding brain.

ONE MG ACTINOMYCIN LC

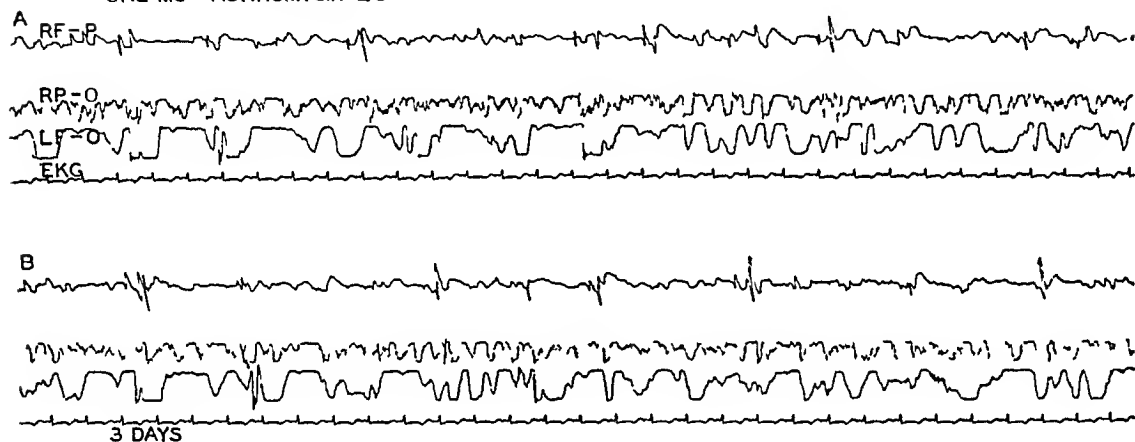


Fig 9—Electroencephalograms taken from a monkey three days after the intracortical injection of 1 mg of actinomycin in the left central (LC) region. The slow waves in the left leads and spiky, irregular activity in the right leads are quite evident. The leads are as follows: RF-P, right frontal and parietal leads, LF-O, left frontal and occipital leads, RP-O, right parietal and occipital leads, EKG, electrocardiogram taken from needle electrodes in the muscles of the two upper extremities. The horizontal line at the base indicates an interval of one second, the vertical line at the right, a calibration of 60 microvolts.

Electroencephalograms made immediately after the application of actinomycin to the cerebral cortex of two cats showed only a few spikes in the leads from the side of the brain in which the injection was made. Records made of 1 monkey three days after the intracortical injection of 1 mg of actinomycin showed conspicuous increase in electrical activity with irregular spikes (fig 9).

It is concluded that actinomycin produces a severe necrobiotic reaction when applied to the cerebral cortex, manifested clinically by apathy, convulsive phenomena and death. The drug appears rather toxic even when given in relatively small doses into the cisterna magna.

## CLAVACIN

Clavacin, an antibiotic substance derived from *Aspergillus clavatus*, is bactericidal to both gram-positive and gram-negative bacteria, but it is highly toxic when administered systemically

Clavacin in granular form applied to the cerebral cortex even in relatively large amounts produces no clinical or electroencephalographic

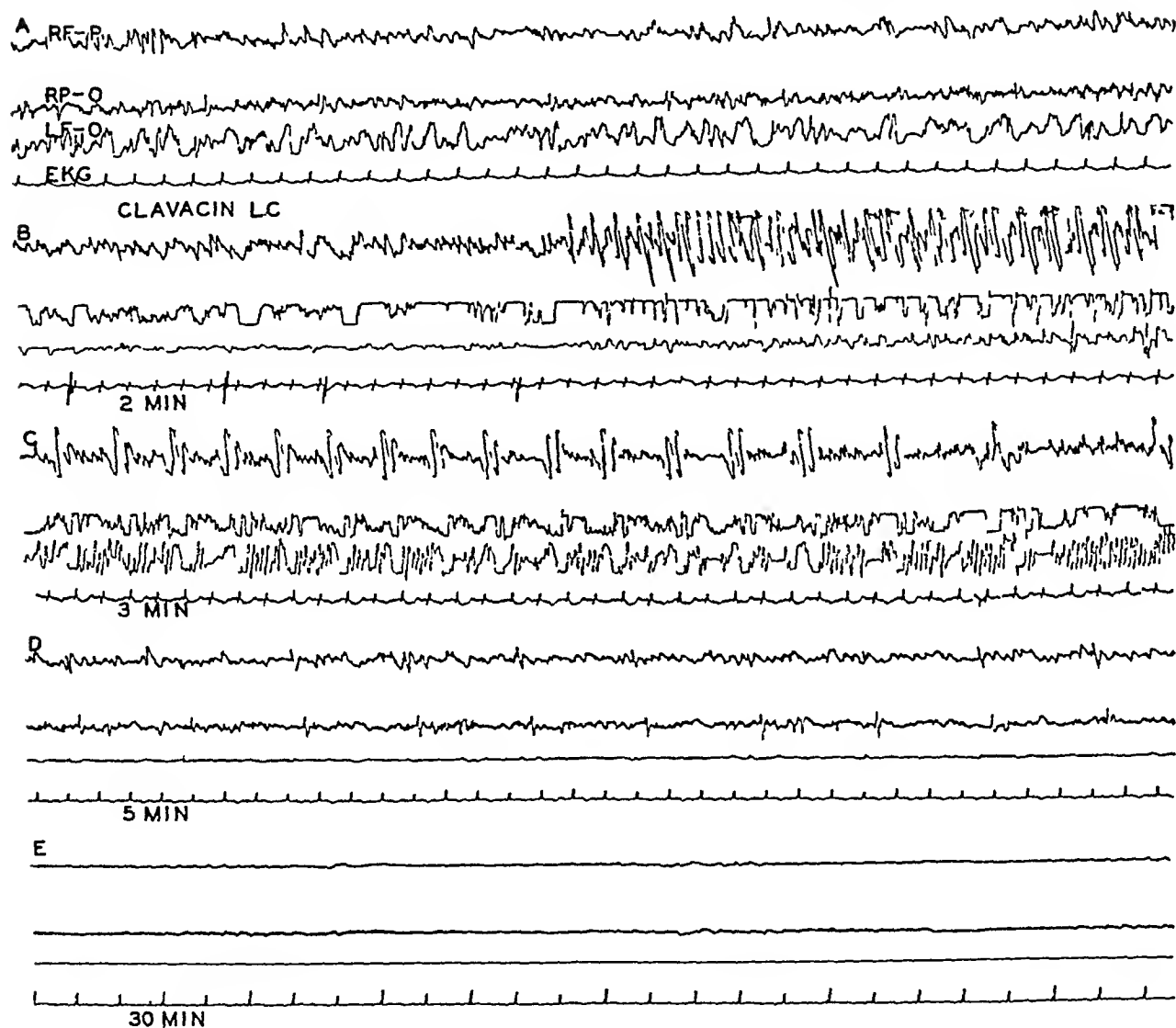


Fig 10—Electroencephalograms taken from a cat prepared with procaine anesthesia, curarized and artificially aerated. The leads are as follow *RF-P*, right frontal and parietal leads, *RP-O*, right parietal and occipital leads, *LF-O*, left frontal and occipital leads, *EKG*, electrocardiogram taken from muscles electrodes inserted in the muscles of both upper extremities

*A*, control record, *B*, record two minutes after the injection of 1 mg of clavacin in the left central (*LC*) region (the convulsive activity is pronounced), *C*, record three minutes after the injection, showing a generalized seizure, *D*, record five minutes after the injection, with decreasing cortical activity and only occasional spikes, *E*, record thirty minutes after the injection, with the cortical activity abolished

The horizontal line at the base indicates an interval of one second, the vertical one at the right, a calibration of 60 microvolts

abnormalities. If, however, the clavacin is dissolved in water by heating and is then applied to the parietal cortex in doses of 5 to 10 mg, pronounced changes occur in the electroencephalogram (fig 10). The normal electrical activity of the cerebral cortex is rapidly dampened, so that twenty minutes after the application of the drug the record is absolutely flat. In 1 cat, after application of 10 mg of clavacin dissolved in 0.5 cc of isotonic solution of sodium chloride severe convulsive phenomena appeared in the electroencephalogram, and within two minutes a major convulsion was recorded electroencephalographically. After this attack the electrical activity on the side of the injection decreased, although diphasic spikes were still present in the leads from the other side. After ten minutes the record was flat.

#### COMMENT

All the antibiotic substances so far examined have shown convulsant propensities when directly applied to the central nervous system in large doses. The intensity of the epileptogenic factor varied with the drug being tested. Comparison of their convulsant effect is difficult, because their antibiotic activities are not equivalent, penicillin being effective largely against gram-positive organisms and streptomycin against gram-negative bacteria. Until the active principles are isolated in chemically pure form, a valid comparison of the convulsant factors is impossible. It seems reasonable to state, however, that penicillin and streptomycin may be applied to the central nervous system without toxic effects in doses far above an adequate antibiotic concentration, whereas streptothricin, actinomycin and clavacin appear to produce severe toxic effects in concentrations little, if at all, above therapeutic levels. It would seem then that the latter antibiotic substances would not be acceptable for clinical use in the central nervous system even if they had no systemic toxic effects. The other drugs, from the standpoint of convulsive effects, would appear to be acceptable for therapeutic application to the central nervous system in antibiotic concentrations. All, however, may give rise to convulsive phenomena if large doses are administered. The margin between the therapeutic concentration and the convulsive threshold is, however, so great that with reasonable care the toxic effects should be avoidable.

#### SUMMARY

Clinical and experimental studies indicate that penicillin may produce convulsive manifestations. During systemic administration for conditions other than primary ones of the central nervous system, the electroencephalogram was found to be abnormal in more than 60 per cent of a series of 51 patients. Control records taken before and after penicillin therapy usually showed normal tracings. Large doses of penicillin

injected intrathecally in man or monkey may give rise to convulsions, followed in some cases by coma and death. The application of as little as 500 international units to the cerebral cortex of the macaque monkey may induce epileptic attacks.

Streptomycin in cats and monkeys applied to the cerebral cortex in doses of 1,250 units induced convulsive manifestations in 30 per cent of the animals. Electroencephalographic records at such times showed slow waves and spikes, with subsequent decrease of cortical activity lasting for one and one-half to three hours. Cisternal injection in the monkey of 2,500 units of streptomycin induced signs of severe cerebellar dysfunction.

Streptothricin applied to the parietal cerebral cortex in doses of 5,000 to 10,000 units produced clinical and electroencephalographic convulsive manifestations. Although these phenomena usually disappeared spontaneously in two to three hours, in 2 monkeys they persisted for two weeks. At necropsy the brains of these animals showed extensive softening with perivascular petechial hemorrhages.

Actinomycin injected into the cerebral cortex or the cisterna magna in a dose of 1 mg after a latent period of nine hours produced severe prostration, fasciculations and convulsions, with death in one to seven days. At the site of injection into the cerebral cortex a severe necrotic reaction with edema and petechial hemorrhages was found.

Clavacin when injected into the cerebral cortex in doses of 5 to 10 mg induced clinical and electroencephalographic manifestations of convulsive phenomena with a marked decrease in spontaneous cerebral activity.

There appears to be a wide margin of safety between the antibiotic concentration of penicillin and streptomycin and the convulsive threshold for those drugs. Such does not appear to be the case for streptothricin, clavacin or actinomycin. Although penicillin has few toxic reactions, if it is given in excessive amounts in the cerebrospinal fluid, severe neural sequelae in the form of radiculitis or convulsions may develop.

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## ABNORMAL DELAY OF VISUAL PERCEPTION

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THE NEED for discovering a nervous disorder as early as possible is obvious. The diagnostic method to be described here utilizes a peculiar visual phenomenon which makes possible recognition of minute unilateral delays in perception of visual impulses. It is expected that this method, which takes advantage of the high degree of sensitivity of visual reception, will promote recognition of the disturbed function of the optic nerve at an earlier state than is obtainable with the existing methods.

Fully aware of the incompleteness of my clinical investigations,<sup>1</sup> which began in 1942 and were interrupted by the exigencies of the war, I present the method for the purpose of further study in competent institutions.

### THE PULFRICH EFFECT

The basic phenomenon is easily observed with the following simple setup. Let a pendulum (some small dark object tied to a thread) swing in front of and parallel with a light vertical background, and either squeeze one eye by an attempt at forceful closing or put a smoked glass in front of one eye. Suddenly the pendulum no longer appears to swing in a plane parallel with the background but seems to describe a horizontal circle, approaching the observer and receding behind its initial, vertical, plane. In other words, a stereoscopic, three dimensional effect is produced by an actually two dimensional movement.

An explanation of this phenomenon, first observed by an astronomer, was made and published by Pulfrich<sup>2</sup> (who paradoxically, was one eyed from childhood and was thus deprived of stereoscopic vision). Reduction of the light entering one eye makes the image on this retina darker than the image on the other retina. It being accepted that of two optic impulses the weaker one is transmitted more slowly, the sensation from the eye with dimmed vision is registered in consciousness a trifle later than the sensation from the unobstructed eye. Under the

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1 This investigation was supported in part by the Jennie Grogan Mendelson Memorial Fund for Ophthalmology and was carried out at the Ophthalmic Research Laboratory, Wayne University College of Medicine.

2 Pulfrich, C. Stereoscopy in the Service of Isochromatic and Heterochromatic Photometry, *Naturwissenschaften* 10 553 (June) 1922.

special experimental conditions, this time difference is transposed into a spatial difference, with resulting stereoeffect

(A detailed description of this "Pulfrich effect" will be presented at the end of this paper)

#### RATIONALE OF CLINICAL APPLICABILITY

In the original experiment, the time difference between perception of the optic impulses on the right and left sides is produced by an objective difference of illumination. The same effect may be expected to occur in spite of identical illumination for the two eyes if the transmission of the impulses between retina and visual cortex is delayed unilaterally, owing to pathologic conditions. This delay, however, may be so minute as to be below the threshold of consciousness, thus necessitating some "magnifying" procedure in order to promote its recognition. Such a procedure was developed along the following line of thought

In normal subjects the Pulfrich effect is induced when the brightness difference for the two eyes has reached a certain magnitude. It is to be expected that the brightness difference required for the effect would be smaller for persons with an already existing "subthreshold" delay in transmission of impulses. Hence it is necessary only to design a simple quantitative method of reducing the intensity of the incident light for either eye.

#### DEVICE FOR CLINICAL INVESTIGATION

In a regular frame for refraction work one pair of polaroid glasses was fitted for each eye. While the polaroids adjacent to the eye were fixed in their positions, the outer polaroids could be rotated, with the angle of rotation easily measured on a scale along the circumference of the frame. The initial position of the outer polaroids was adjusted for maximal transmission of light. Rotation of either—right or left—outer polaroid resulted in gradual darkening of any desired degree, with a defined relation to the angle of rotation.

The apparatus<sup>3</sup> consisted of a framed square of frosted glass, an electric light behind the glass produced the illumination of the screen, in front of which, in the lower half of the field, a vertical black rod moved with constant, but variable, speed from one side of the frame to the other, to and fro. This rod was driven by an electromotor, the speed of the movement was controlled by a resistance and measured by means of a modified taximeter checker. A fixed metal rod attached to the center of the upper frame extended vertically downward into the upper half of the field. The lengths of the fixed and of the movable rod were so adjusted that the lower rod when passing its midway position appeared to be the direct continuation of the upper rod.

This fixed rod serves two purposes. It is the fixation point for the observer, and it marks the virtual center of the apparent circle described by the moving rod when the stereoeffect becomes manifest.

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3 Manufactured by the Nichols-Chase Company, Detroit



## PROCEDURE OF TESTING FOR PULFRICH EFFECT

Since a normal observer serves as the standard of comparison, the extent of darkening required to elicit the stereoeffect is determined for each eye of the investigator before the patient is examined (This value remained amazingly constant, as recorded over a period of five months) It is advisable to have the rotation of the movable polaroid made by an assistant, at least in the beginning, in order to avoid the pitfall of training muscle and posture sense of the rotating fingers, tending to stop the rotation always at the same position It is also essential to proceed rather fast from the initial position of the polaroid When the darkening proceeds at a slow pace, the threshold is "driven", the observer is fatigued, and it becomes difficult to decide where the stereoeffect began

The observer should be seated at such a distance from the apparatus that the two rods can be clearly recognized For an observer with emmetropic or corrected vision a distance of approximately 6 feet (180 cm) proved satisfactory With myopic subjects, if no eyeglasses are worn, the distance must be reduced

For a given brightness difference between the eyes, the Pulfrich effect becomes more intense the faster the movable rod travels through the illuminated field There is, however, a speed limit to this intensification when fatigue and blur intervene Hence it is important to select a speed which is favorable for an impressive stereoeffect and to keep this speed constant throughout the test

Testing proceeds in the following steps

- 1 The room is darkened, and the frosted glass is illuminated
- 2 The normal observer, at the chosen distance, adjusts the outer, movable, polaroids for maximal transmission of light while looking at the illuminated screen The numerical value of this starting position is recorded
- 3 The motor is turned on and kept at convenient speed
- 4 The outer polaroid of one eye is rotated until the Pulfrich effect appears The angle of rotation is recorded and the test repeated from three to five times

The same procedure is carried out with the other eye

Before the patient undergoes the testing, the following factors must be determined

- 1 Whether the pupils are of equal width Although slight or even moderate, anisocoria did not seem to influence the threshold of the Pulfrich effect, a considerable pupillary difference will create such difference in retinal brightness as to influence the stereoeffect Similarly, corneal opacities or cataract may interfere with the test
- 2 Whether the patient when looking at the illuminated glass with both eyes and alternately with either eye experiences any difference of brightness sensation between his eyes If he does, the test cannot be applied
- 3 Whether the patient when looking at the screen with the rod in motion but without polaroids experiences the Pulfrich effect There are persons who do, and from the direction of the apparent circular movement—whether clockwise or counterclockwise—the side of the transmissional delay can be determined<sup>4</sup>

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4 The phenomenon is explained in connection with the figure

- 4 Whether the patient experiences the Pulfrich effect at all There are not infrequently persons who, in spite of extreme brightness difference and high speed of the moving rod, fail to experience the Pulfrich effect This failure may be caused by any of the following conditions
- (a) The capacity for stereopsis may be totally lacking (In this connection, it is worthy of note that persons tested in this series showed normal stereopsis [stereoscopic picture test] but did not exhibit the Pulfrich effect)
  - (b) When perception of movement is impaired it is likely to involve perception of the Pulfrich effect
  - (c) People do not see what they do not expect to see or are not used to seeing Hence it is of prime importance to demonstrate the stereoeffect as impressively as possible to the patient before the quantitative testing starts, by creating a distinct brightness difference between the two eyes

#### DEFINITION OF "NORMAL," "QUESTIONABLY ABNORMAL" AND "ABNORMAL" PULFRICH EFFECT

The Pulfrich effect was considered normal for differences of rotation up to 15 degrees from the normal observer, since difference of this magnitude occurred in the majority of patients With differences over 15 and under 25 degrees the Pulfrich effect was called "questionably abnormal" The effect was considered "abnormal" when the patient required consistently in all 3 trials or in 3 out of 5 trials at least 25 degrees less rotation of the polaroid than does the normal observer

#### RESULTS

Seventy-four male patients (white persons and Negroes) were examined in order to obtain some idea of the quantitative aspect of the Pulfrich effect, no attempt was made to select patients with such conditions as would most likely involve the visual sector All patients were inmates of Eloise Hospital

They presented the following diagnoses

	No of Patients
Alcoholism, chronic	4
Amyotrophic lateral sclerosis	1
Brain tumor (questionable)	2
Cerebellar ataxia	1
Convulsive disorder	3
Tumor of spinal cord	1
Senile dementia	1
Diabetes mellitus	1
Extirpation of right parieto occipital subcortical area (gumma)	1
Dementia paralytica	3
Hemiplegia	5
Idiopathic epilepsy	1
Cerebral spastic infantile paralysis (Little's disease)	2
Cerebrospinal syphilis	5
Syphilis (peripheral neuritis)	1
Atrophy of optic nerve	1
Postencephalitic paralysis agitans	3
Basophilic adenoma of the pituitary	1
Polycythemia vera	1
Cerebellopontile tumor	1
Multiple sclerosis	4
Tabes dorsalis	16
Tabetic form of dementia paralytica	2
Condition undiagnosed at the time of testing	13
Total	74

Testing these patients for the Pulfrich effect produced the following results

1 Five patients demonstrated an abnormal Pulfrich effect. They presented the following diagnoses: tabes dorsalis, 2 patients; tabetic form of dementia paralytica, 1 patient; chronic alcoholism, 1 patient; and diabetes mellitus, 1 patient.

2 In 1 patient with tabes dorsalis there was a questionably abnormal Pulfrich effect.

3 In 1 patient with the diagnosis of "convulsive disorder" the Pulfrich effect became less distinct when the speed of the moving rod was decreased, in contrast to the normal situation, in which speed enhances perception of the stereoeffect.

4 In 2 patients the Pulfrich effect could be elicited for the one eye only. The condition of 1 of these patients was undiagnosed at the time of the testing. He was very intelligent, the pupils were of equal width, and stereopsis was present. The other patient offered a diagnostic problem, suggestive of cerebral tumor, syphilis of the central nervous system, chronic alcoholism or subdural hemorrhage. His vision was reduced, and the pupils were round, the left being smaller than the right. When the right eye was darkened, the Pulfrich effect was clearly experienced, but no degree of darkening of the left eye or any variation of speed was capable of eliciting the Pulfrich effect. This patient, too, had unimpaired stereopsis.

5 Seventeen patients did not experience the Pulfrich effect at all. For these patients the diagnoses were as follows: multiple sclerosis, 1; syphilis of the central nervous system, 2; postencephalitic paralysis agitans, 2; basophilic adenoma of the pituitary gland, 1; polycythemia vera, 1; dementia paralytica, 1 (this patient showed anisocoria, which, however, had failed to facilitate the Pulfrich effect); idiopathic epilepsy, 1; and senile dementia, 1. One patient was a girl of 13, with nausea, severe headache and oculomotor palsy. One patient was examined nineteen days after extirpation of a subcortical gumma in the right parieto-occipital area; his stereopsis was unimpaired.

For 5 patients no diagnosis had been made at the time of the testing. Three of them appeared to have normal stereopsis, but in the fourth the existence of stereopsis remained in doubt.

6 Twelve patients were so inconsistent or noncooperative that no evaluation of their results was possible.

7 The remainder, of 36 patients, matched the Pulfrich threshold of the normal observer.

## COMMENT

*Site of the Normal Pulfrich Effect*—The most likely site of the Pulfrich effect is a synaptic delay in conduction of the optic impulse at the level of the retinal ganglion cells

*Origin of the Abnormal Pulfrich Effect*—The abnormal Pulfrich effect may indicate an intensified synaptic delay. It is premature to theorize on the causes of such delay, i e., whether the electrical or the chemical factors involved in the transmission of impulses have undergone changes. Clinically it has been known for decades that in cases of tabes the perception of pain resulting from peripheral stimulation may be considerably delayed.

Another possible cause of the abnormal Pulfrich effect is demyelination of the nerve fiber itself, with consecutive slowing of conduction.

A study of the correlation between the abnormal Pulfrich effect and neurohistopathologic changes is highly desirable but may encounter difficulties. The "sensitivity" of the Pulfrich effect is high—it is possible to register differences of less than 0.001 second between visual sensation on the right side and that on the left—and this indication of deteriorating function may well precede the histochemically demonstrable changes of structure.

Another field of study is the correlation of the Pulfrich effect, stereopsis and perception of movement. The setup for eliciting the Pulfrich effect is flexible, lending itself to many modifications and being capable of both a high degree of accuracy and technical simplicity for clinical studies.

The influences of dark adaptation and pupillary dilation on the quantitative outcome of the rotation of the light-reducing polaroid remain to be studied.

Dark adaptation of the darkened eye would increase the apparent brightness, while the pupillary dilation would tend to counteract the reduction of intensity of the incident light. It is unknown to what extent the speed of transmission of impulses depends on (1) the physical intensity of the light stimulus and (2) the state of adaptation, i e., the intensity of the sensation. It appears, however, from the uniformity of values for the same observer, as well as from the agreement among many other observers, that any modification introduced by adaptation and pupillary reflex is accounted for by an allowance of up to 15 degrees of rotation. When the outer polaroid is rotated rapidly and the judgment is made accordingly, the influence of adaptation is made negligible. As to the pupillary reaction, it may prove advantageous to employ an artificial pupil in front of each eye.

*Analysis of Cases*—Only a superficial analysis of the results for the relatively small number of patients is possible.

The largest number of subjects with an abnormal or a questionably abnormal Pulfrich effect is found among tabetic patients. All these patients exhibited the Argyll Robertson phenomenon, in 3 of them the pupils were of equal size, while in a fourth the right pupil was barely appreciably smaller than the left. The 2 other, nontabetic, patients reacted normally to light. This predominance of tabetic patients may be significant, however, it must be remembered that the number of patients with the diagnosis of *tabes dorsalis* and the tabetic form of *dementia paralytica* by far exceeds that of the patients with any other disease examined.

One of the patients with a convulsive disorder had undoubtedly some visual disturbance. He recognized the rod when in movement or in the resting position but complained of haziness of the outlines. Whereas normally the Pulfrich effect is enhanced by increasing the speed of the moving rod, the opposite phenomenon—enhancement by decreasing the speed—was observed in this patient. This paradoxical reaction could be explained on the basis of impaired perception of movement, which increases with increasing speed. Within a limited range, perception of the moving rod was adequate to assure the Pulfrich effect.

An explanation of the seemingly queer phenomenon in the 2 patients exhibiting the effect in one eye only cannot be offered. The presence of the Pulfrich effect when the one eye was darkened and its absence when the other eye was darkened would theoretically mean that, although stereovision exists when, say, the right eye receives less light than the left eye, the patient cannot maintain stereovision if the other (left) eye receives less light. I know of no experiments in which static stereopsis has been studied under conditions of brightness differences for the right and for the left eye.

#### CONCLUSIONS

The assumption has been confirmed that unilateral delay of perception of visual impulses can be demonstrated with simple means which transpose the time difference into a spatial pattern.

The presence of such unilateral delay may be the first sign of a lesion in one optic nerve.

The simplicity and sensitivity of the described method promise to facilitate the discovery of pathologic changes at an early state.

In the diagram,  $SS$  indicates the plane of the illuminated background (screen),  $n$ , the position of the fixed metal rod, extending from the upper frame, and  $m \rightarrow m \leftarrow m$  the moving rod entering the visual field from the left, coinciding with the position of the fixed rod midway and returning from the right. The left ( $A_1$ ) and the right ( $A_2$ ) eye look at the fixed rod  $n$ , as designated by the lines of vision  $A_1 n$  and  $A_2 n$ . A darkening device is indicated in front of the left eye  $A_1$ .

When the moving rod on its way from the left to the right is localized at  $m'_2$  by the right eye,  $A_2$ , the delayed perception of the left eye results in a lag, so that the moving rod is localized for the "slower" eye at  $m'_1$ , this double localization, however, produces not two images, but one image, localized at the intersection of  $A_1 m'_1$  and  $A_2 m'_2$ , in  $m'$ , behind the plane of actual movement. At the two points of reversal of movement, when the rod comes to a standstill, the two eyes localize the rod at the same place. When the rod returns from the right point of reversal, the right eye sees the rod at  $m''_2$ , while the left eye localizes

GRAPHIC DESCRIPTION OF THE PULFRICH EFFECT (FIGURE)

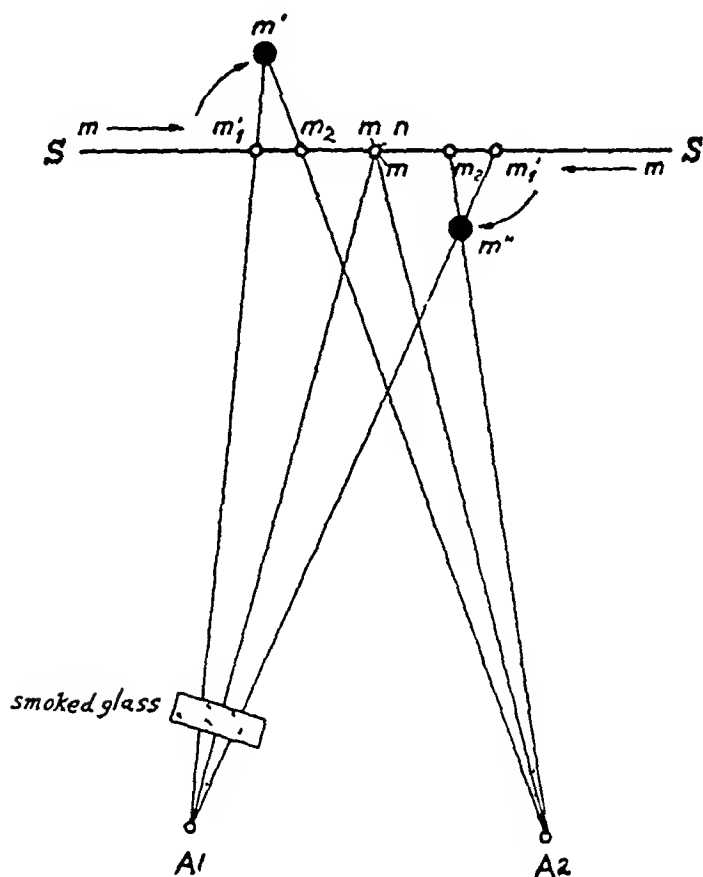


Diagram of the Pulfrich effect (after Pulfrich<sup>2</sup>)

the rod at  $m''_1$ , binocular localization occurs at  $m''$ , in front of the plane  $SS$ , at the point of intersection of  $A_1 m''_1$  and  $A_2 m''_2$ . Thus, a clockwise movement results from delaying the perception of the left eye, and a counterclock movement, from delaying perception of the right eye.

#### SUMMARY

When a normal observer looks at a pendulum swinging in front of an illuminated background and a smoked glass is placed in front of one eye, the pendulum appears suddenly to describe a horizontal circle. This stereoeffect—the so-called Pulfrich effect—results from

a lag of perception originating in the eye behind the smoked glass. The physiologic basis of the Pulfrich effect is probably the slower conduction of impulses and/or transmission of the weaker of two, otherwise identical, stimuli.

This normal Pulfrich effect is elicited by a brightness difference of certain magnitude between the illuminations of the two eyes. It is assumed that in persons with a pathologic condition of one optic nerve abnormal delay in conduction and/or transmission of impulses may be an early occurrence. This delay, however, at its early stage, may be below the threshold of perceptibility, requiring a special "magnifying" device for demonstration.

The assumption is made that for persons with such subthreshold delay the light intensity for the eye on the affected side requires less reduction than for a normal observer in order to make the Pulfrich effect manifest.

A simple method of producing and measuring the Pulfrich effect by means of a moving rod and two pairs of polaroids is described.

Examination of 74 patients selected at random revealed the actual existence of abnormal unilateral delays in 5, possibly 6, patients.

Relations of the Pulfrich effect, static stereopsis and perception of movement and the site and cause of the abnormal Pulfrich effect are discussed, and the study of correlations between the abnormal effect and histopathologic changes is suggested.

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# DOMINANT BRAIN WAVE FREQUENCIES AS MEASURES OF PHYSICOCHEMICAL PROCESSES IN CEREBRAL CORTEX

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AND

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IT IS now well known that the electroencephalogram is modified by a variety of factors influencing the physicochemical environment of the brain. Studies of the effects of such agents as carbon dioxide, oxygen tension, blood sugar, temperature and drugs have been made by many investigators on the measurable variables per cent time present of the alpha activity, delta index, dominant frequency (usually the alpha frequency), wave amplitude or voltage and the form of the frequency spectrum. In this paper we point out why we believe that one of these measures is superior to the others for furnishing information about the chemical dynamics of the cortex and show why some current methods of analysis of frequencies in the electroencephalogram, while empirically interesting, must give discrepant results when compared with other methods.

The most conspicuous aspect of the normal electroencephalogram is usually the alpha rhythm. This is a rhythm of a specific frequency, characteristic of the individual subject, of from 8 to 13 cycles per second. The waves are easily recognized in most records and are of sinusoidal form. The constancy of their frequency for a given person suggests their production by basic, constant chemical dynamics. The alpha frequency per se is little affected by sensory stimuli, and in this way it is in sharp contrast to measures of the amount of time the alpha waves are present in the record, i e., to the "per cent time alpha activity". For example, when the eyes are open, the alpha frequency is the same as, or perhaps  $\frac{1}{2}$  cycle faster than, it is when they are closed, but the per cent of time the alpha activity is present is greatly decreased, or the rhythm may even be eliminated for a time, when the eyes are open.

In like manner, it is a commonplace experience of students of the electroencephalogram to find in a given group of relaxed subjects with closed eyes, all of whom show a clearly countable alpha frequency of, say, 10 cycles per second, that these waves may vary from 10 to 90 per

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cent in the percentage of time they are present. Thus, the frequency of the alpha rhythm and the per cent of time it is present are independently variable and must therefore be controlled by quite different mechanisms. Any method of analysis that fails to recognize this and measures these two variables indiscriminately is not in a position to delineate underlying determinants of either one, despite the empiric changes it may reveal in gross properties of the brain waves when the chemical environment of the brain is modified by physiologic agents.

It is generally accepted that the amplitude of the waves is a rough measure of the number of cellular units contributing to the voltage. The frequency of the waves has been shown to be determined by quite different factors, which we shall discuss. Little is known about the mechanism underlying the percentage of time the alpha waves are present beyond the unproved hypothesis that it depends on the synchrony of the units contributing to the response, which is destroyed by afferent stimulation. Why some people have much and others little or no alpha activity is unknown.

Frequency in terms of waves per second is by definition a rate, and one is tempted to ask, a rate of what? In a series of papers, beginning in 1936, one of us (H. H.) and collaborators investigated this problem by studying the relation of the dominant, or alpha, frequency to aspects of cerebral metabolism. It was shown that the alpha frequency in man, when studied in relation to the internal body temperature (by means of diathermy) follows the Arrhenius equation known to describe the velocity of chemical reactions as a function of temperature. Of much more significance was the observation that the activation energy, or temperature characteristic, of the alpha rhythm calculated from this equation gave three values, each one of which has frequently been encountered in measurements of oxidation rates of cell suspensions and tissue slices *in vitro*.<sup>1</sup> We have been able to identify two of these values with specific enzyme systems extracted from tissues.<sup>2</sup> One corresponds to the activation energy of the oxygen-activating cytochrome system prominent in most tissues, including brain, and the other, to the no less important dehydrogenase enzyme that converts succinate to fumarate, thereby furnishing hydrogen to combine with

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<sup>1</sup> Hoagland, H. Pacemakers of Human Brain Waves in Normals and in General Paretics, *Am J Physiol* **116** 604-615, 1936, Some Pacemaker Aspects of Rhythmic Activity in the Nervous System, in *Cold Spring Harbor Symposia on Quantitative Biology*, Cold Spring Harbor, N. Y., The Biological Laboratory, 1936, vol. 4, pp. 267-284.

<sup>2</sup> Hadjidian, Z., and Hoagland, H. Chemical Pacemakers. I. Catalytic Brain Iron, II. Activation Energies of Chemical Pacemakers, *J. Gen. Physiol.* **23** 81-99, 1939, III. Activation Energies of Some Rate-Limiting Components of Respiratory Systems, *ibid.* **24** 339-352, 1941.

the cytochrome-activated oxygen. The third value of activation energy for alpha brain wave frequencies has not as yet been related to any specific enzyme system. This last value characterizes the normal electroencephalogram. The values corresponding to succinodehydrogenase and to the cytochrome system were encountered at various advancing stages of dementia paralytica. These results could be accounted for satisfactorily by the view that the frequency of the alpha rhythm is directly proportional to the velocity of a chemical pacemaker or bottleneck in the serial chain of enzyme-catalyzed events involved in cerebral respiration. Syphilitic encephalitis apparently alters the relative velocities of various steps in cerebral respiration, so that with the progression of the disease the slowest step in the respiratory chain shifts, with the result that first one, and later another, step becomes the chemical pacemaker. Our studies of the relation of alpha frequencies to the sugar<sup>3</sup> and oxygen<sup>4</sup> of the blood, to dinitrophenol<sup>5</sup> and to thyroxin<sup>6</sup> all were consistent with these general observations.

It should be made clear, however, that it is the change in the alpha frequency that is proportional to the change in the cellular respiration. The absolute rate, e g., 10 cycles per second, is contingent on the electrical constants of the tissues as well as on the respiratory rate of the cells, and these constants are only indirectly related to oxidative events. A recent review of the work on chemical pacemakers in relation to the frequencies of physiologic events has been made by Hoagland.<sup>7</sup>

In the studies previously mentioned, frequencies were obtained by simply counting the number of alpha waves per second in the records with dominant alpha activity for large samples and averaging, so that mean values statistically significant to 0.1 cycle per second were obtained.

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3 Hoagland, H., Rubin, M. A., and Cameron, D. E. Electroencephalogram of Schizophrenics During Insulin Hypoglycemia and Recovery, *Am J Physiol* **120** 559-570, 1937.

4 Himwich, H. E., Hadidian, Z., Fazekas, J. F., and Hoagland, H. Cerebral Metabolism and Electrical Activity During Insulin Hypoglycemia in Man, *Am J Physiol* **125** 578-585, 1939.

5 Hoagland, H., Rubin, M. A., and Cameron, D. E. Brain Wave Frequencies and Cellular Metabolism. Effects of Dinitrophenol, *J Neurophysiol* **2** 170-172, 1939.

6 Rubin, M. A., Cohen, L. H., and Hoagland, H. The Effect of Artificially Raised Metabolic Rate on Electroencephalogram of Schizophrenic Patients, *Endocrinology* **21** 536-540, 1937.

7 Hoagland, H. Chemical Pacemakers and Physiological Rhythms, in Alexander, J. *Colloid Chemistry*, New York, Reinhold Publishing Corporation, 1944, vol. 5, pp. 762-785.

Recently, Engel and collaborators<sup>8</sup> have used a new method of frequency analysis in studies of effects of physiologic agents on the electroencephalogram. This method is different from that which we have used for defining and measuring the dominant frequency, and quantitative agreement between the methods could not be expected. Brazier, Finesinger and Schwab,<sup>9</sup> on the other hand, have developed what seems to us a more satisfactory method of dealing with the electroencephalographic spectrum, based on studies of the dominant frequency or frequencies. Their method usually yields a main dominant frequency identical with the alpha rhythm as we have studied it. Since we have found that quantitative changes in such frequencies may serve as a direct key to underlying chemical kinetics, we wish to compare these methods and to show that the frequency analysis of Engel and associates, while empirically interesting and superficially similar to that of Brazier and Finesinger, actually measures a combination of two independent variables and is not suitable on theoretic grounds for use in delineating controlling kinetic events as rates within the cells.

#### METHODS

Engel and associates described their method of analysis of the frequency spectrum of the electroencephalogram as follows:

With the usual ruled paper (large divisions at one second intervals),\* the number of complete waves in each one second strip of record was counted. The count for the total of 300 one second intervals was made, and the distribution of frequencies per second was expressed as a percentage of the whole. Stretches of low voltage fast activity, which were present in varying degrees in all records, were designated as such, and no attempt was made to estimate the individual waves, which were often not countable. When a given interval contained both countable waves and low voltage fast activity, the type which occupied

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8 (a) Engel, G. L., Romano, J., Ferris, E. B., Webb, J. P. and Stevens, C. D. A Simple Method of Determining Frequency Spectrums in the Electroencephalogram, *Arch Neurol & Psychiat* **51** 134-146 (Feb) 1944. (b) Romano, J., and Engel, G. L. Delirium. I. Electroencephalographic Data, *ibid* **51** 356-377 (April) 1944. (c) Engel, G. L., and Romano, J. Delirium. II. Reversibility of the Electroencephalogram with Experimental Procedures, *ibid* **51** 378-392 (April) 1944. (d) Engel, G. L., and Rosenbaum, M. Delirium. III. Electroencephalographic Changes Associated with Acute Alcoholic Intoxication, *ibid* **53** 44-50 (Jan) 1945.

9 (a) Brazier, M. A. B., and Finesinger, J. E. Characteristics of the Normal Electroencephalogram. I. A Study of the Occipital Cortical Potentials in 500 Normal Adults, *J Clin Investigation* **23** 303-311, 1944. (b) Brazier, M. A. B., Finesinger, J. E., and Schwab, R. S. Characteristics of the Normal Electroencephalogram. II. The Effect of Varying Blood Sugar Levels on the Occipital Cortical Potentials in Adults During Quiet Breathing, *ibid* **23** 313-317, 1944. (c) III. The Effect of Varying Blood Sugar Levels on the Occipital Cortical Potentials in Adults During Hyperventilation, *ibid* **23** 319-323, 1944.

the greater portion of that interval was arbitrarily selected for purposes of designation

Such an analysis yields a "spectrum" of frequencies ranging from 1 to 12 per second, together with some low voltage activity. It should be emphasized, however, that this is not a true spectrum of frequencies in that the percentages of one second intervals containing 8 waves, 9 waves, 10 waves, etc., rather than the percentages of 8 per second waves, 9 per second waves, 10 per second waves, etc., are given. In other words, the distribution of waves per second, rather than the distribution of individual wavelengths, is determined. The latter is a tedious process and involves measurement of the length of each wave with a caliper of some sort. Our method may give a slightly false impression of the distribution of wavelengths greater and less than the dominant one, for waves of these frequencies will tend to be averaged with waves of the dominant frequency and hence may appear in somewhat lower proportion than is actually the case. For example, if 2 or 3 waves of 5 per second frequency should appear with 8 per second waves in a one second interval, the number of waves in that interval would be recorded as 6 or 7, and the figure would not reveal the presence of 5 per second waves. This will not obscure any shift toward faster or slower frequencies, and no error in interpretation will result if it is remembered that the method gives the distribution of average frequencies per second rather than the distribution of wavelengths.

Brazier and Finesinger<sup>9a</sup> described their method as follows

In order to compile a frequency distribution curve, a 2-minute record is first inspected for the presence of artefacts. Any portion showing artefacts due to eye-blinks, muscle movements, etc., is omitted from the sample for analysis. The remainder is measured for total length of time, and this figure becomes the total on which all percentages are calculated.

A transparent grating, marked off in intervals equivalent to each of the frequencies, is then laid on the record, and the frequency of any chains of waves is thus easily determined. The time covered by waves of each frequency is then totaled, the results being expressed as percentages of the whole period measured.

## RESULTS

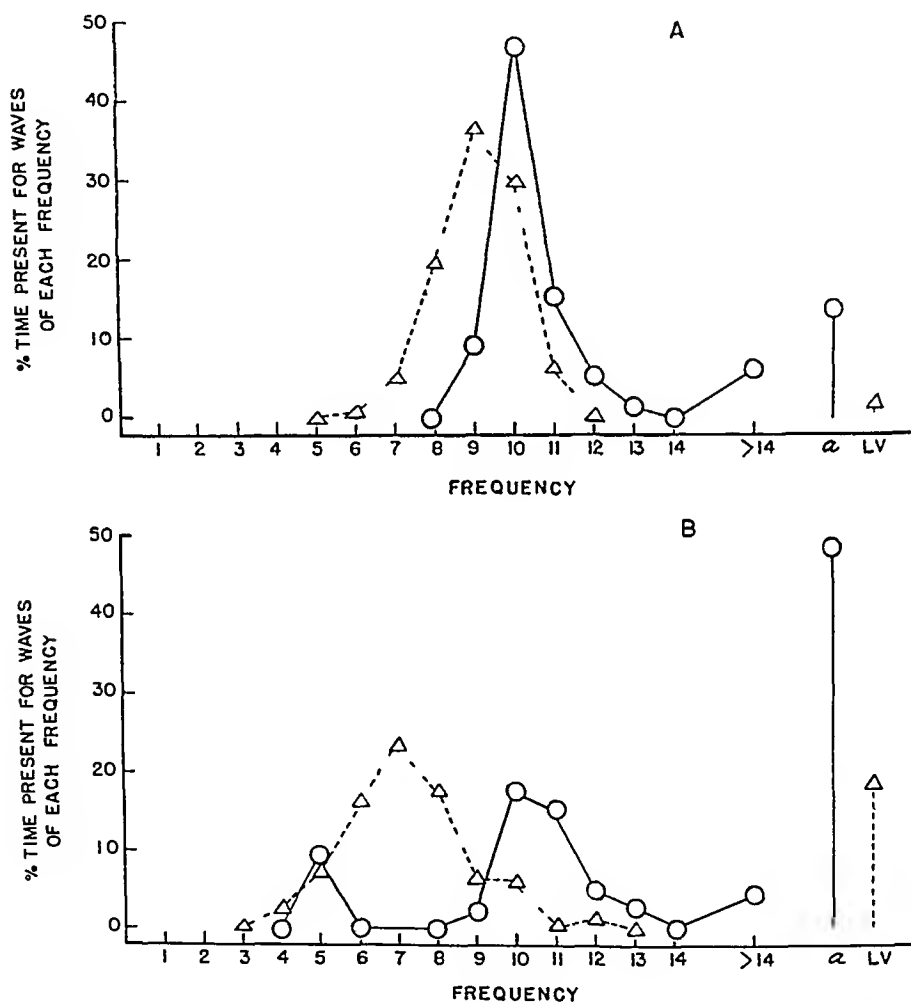
Results of both these methods can best be expressed graphically as plots, in which frequency of waves, as the abscissa, is plotted against the percentage of time the particular frequency is present, as the ordinate. Both show a dominant frequency, but the two methods measure quite different things, owing to the different definitions of frequency involved. Brazier's method yields a dominant frequency that corresponds to a true rate. Engel's method yields a measure that is a composite of frequency and per cent of time the frequency is present. Since it thus lumps into one numerical unit at least two quite independent processes, it cannot serve as an index of rates of change of underlying chemical mechanisms.

This may best be illustrated by applying the two methods to identical sections of the same record and comparing the results.

Electroencephalograms were taken on one of us (D. K.) for five minutes with the subject's eyes closed and immediately afterward for

five minutes with his eyes open. Standard recordings were made from bipolar leads from the right and the left occiput. The same parts of the records were analyzed by the Engel method and by the Brazier method, and the chart shows the results.

With the eyes closed the Brazier method shows a dominant alpha frequency of 10 cycles per second, and this frequency, qua frequency, is not significantly changed by opening the eyes, but it drops from 46.5



*A*, analysis of five minutes of a recording taken when the eyes were closed, with the Brazier method (solid line and circles) and with the Engel method (dotted line and triangles). *B*, similar analysis of another five minute recording taken immediately after *A* was obtained, with the eyes open.

$\alpha$  refers to arrhythmic waves (Brazier method), and *LV*, to low voltage fast waves (Engel method). For discussion, see text.

to 14.2 per cent of time present when the eyes are opened. In this record a 5 cycles per second rhythm also appears when the eyes are open. The dominant frequency as analyzed by the Engel method is 9

cycles per second with the eyes closed and as 7 cycles per second when they are opened

Since opening the eyes greatly decreases the per cent of time the alpha activity is present without altering the frequency, and since the Engel method counts as frequency the total number of heterogeneous waves within a second interval, a decrease in the per cent of time the dominant frequency is present would inevitably give fewer waves per second with the Engel method, resulting in an apparent lowering of the dominant frequency. The Engel method introduces into the measurement of frequency the process concerned with determining the per cent of time the frequency is present, and since the mechanism underlying this is clearly independent of the mechanism determining

*Dominant Frequencies in Electroencephalograms of Four Subjects Taken on Five Different Occasions*

Subject	Date (1945)	Dominant Frequency, Engel Method ( $\pm 0.5$ Cycle)	Dominant Frequency, Brazier Method ( $\pm 0.5$ Cycle)	% Time Present of Dominant Frequency, Brazier Method
J D	4/12	8	10	40
	4/14	8	10	38
	4/18	8	10	42
	4/19	8	10	41
	4/21	7	10	35
I C K	4/11	10	10	63
	4/16	10	10	71
	4/17	9	10	56
	4/18	10	10	72
	4/19	9	10	58
I M	4/16	8	10	40
	4/19	7	10	18
	4/21	8	10	52
	4/23	7	10	29
	4/25	9	10	61
A T	4/18	8	11	49
	4/19	8	11	48
	4/21	8	11	52
	4/23	8	11	56
	4/24	7	11	35

the frequency itself, it is apparent that the two methods are not concerned with the same basic phenomenon.

The table shows dominant frequencies of the electroencephalograms taken on five occasions from each of 4 subjects. The dominant alpha rhythm is constant for each subject, but analysis by the Engel method shows day to day variation in their dominant frequency. This variation is due to variation in the percentage of time the alpha rhythm is present, as may be seen from the table. Low per cent time alpha gives a low value for the dominant frequency, high per cent time alpha yields a higher dominant frequency.

#### COMMENT

Engel and associates<sup>81</sup> (page 135) note that their method "may give a slightly false impression of the distribution of wavelengths greater and less than the dominant one" since they do not measure

wavelength but take as the frequency the total number of waves per second. Our main criticism is that the method is misleading in its misuse of the concept of the dominant frequency itself if one considers waves of similar length arranged in sequences as reflecting physico-chemical processes in the cells. Engel and his collaborators are concerned with the effects of physiologic agents on the electroencephalogram, and, while empiric changes are of course brought out by their method, it seems unfortunate to employ a tool which by its very nature, through its definition of "frequency," masks the possibility of a rational interpretation of rates of events going on in the brain.

The dominant frequency as studied with the Brazier method is the frequency which we have used in our earlier studies of the effects of physicochemical agents on the electroencephalogram. It would, for example, be quite impossible on theoretic grounds to calculate meaningful energies of activation of enzyme steps in the carbohydrate cycle with the method of Engel and associates, since their frequencies, including their dominant frequencies, are composed of waves of different lengths and the independent variable, the per cent time alpha, contributes to the determination of their actual frequencies per se.

This may be illustrated by a hypothetical example. Suppose one has a record composed of continuous and uniform sine waves of 10 per second produced by a piece of electrical apparatus. There would thus be only one frequency, the dominant one determined by the properties of the apparatus making the signals. One may now consider an equal length of record consisting of five second strips of the same 10 per second waves, alternating with equal intervals with no waves at all. Such a record could be made artificially by turning the apparatus that makes the waves on and off at five second intervals. The dominant rhythm in both these records, according to our studies and to the Brazier method, is clearly 10 cycles per second, the dominant rhythm according to the Engel method is 10 per second in the first record and 5 per second in the second record, and from this one would be led to the erroneous conclusion that the apparatus producing the waves with a frequency of 5 per second was operating at half its former rate.

For the reasons we have discussed, the measurements of Engel and associates cannot reflect the rates of changes of kinetic processes in the brain, and in effect they mask these processes. The Engel spectrum is a graphic representation of gross qualitative changes observed in the records, and as an analytic instrument it has all the limitations of the delta index,<sup>3</sup> which we have described and have used as a purely empiric expression of the numerical representation of the magnitude of slow wave activity in the electroencephalogram. Quantitative changes with physiologic variables of bands of waves of equal length (e g, the

alpha waves) have led to significant insight into the chemical kinetics of the brain, and further studies along these lines hold promise. Much of the value of this type of investigation may be lost unless the limitations of the methods used are borne in mind.

#### SUMMARY

Use of the dominant alpha frequency as a measure of chemical kinetics of cerebral processes is discussed.

Advantages of the method of Brazier and Finesinger for plotting electroencephalographic frequency spectrums are considered and compared with those of the method of Engel and associates.

It is concluded that the Engel method does not furnish a concept of frequency that lends itself to analysis of the chemical kinetics of cerebral processes.

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# IS RESTORATION OF INHIBITED CONDITIONED REACTIONS BY INSULIN COMA SPECIFIC FOR PAVLOVIAN INHIBITIONS?

Contribution to the Theory of Shock Treatment

ERNST GELLHORN, M D  
MINNEAPOLIS

**I**N a series of papers by Gellhorn and collaborators<sup>1</sup> it was shown that insulin hypoglycemia, especially in the form of insulin coma, and chemically or electrically induced convulsions lead to a restoration of inhibited conditioned reactions. In this work, conditioning of the escape reaction resulting from subjection of the experimental animal (rat) to a slight electric shock was accomplished by the simultaneous presentation of various sensory stimuli. After the conditioned reaction had been fully established, it was gradually inhibited by lack of reinforcement (Pavlov's internal inhibition). Spontaneous recovery of such inhibited reactions did not occur, but a restoration could be induced with great regularity if the animals were subjected to insulin coma and related forms of "shock treatment."

Furthermore, it was observed<sup>2</sup> that if two or more conditioned reactions were studied in the same animal insulin coma and related forms of "shock treatment" acted only on the inhibited conditioned reactions but did not alter the positively established conditioned reactions. However, before a generalization of this statement was suggested, it seemed desirable to investigate a positively established conditioned reaction which in outward appearance was similar to the inhibited conditioned reaction used previously. If it were possible to show that a

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Aided by a grant from the Josiah Macy Jr. Foundation

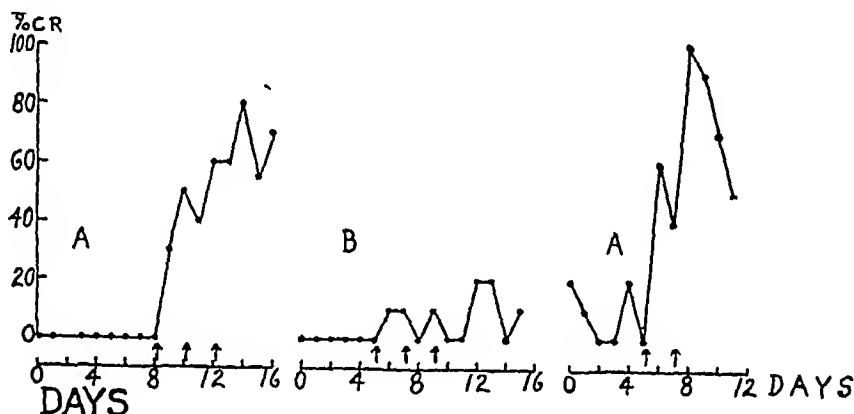
From the Division of Neurophysiology, Department of Physiology, University of Minnesota Medical School

1 (a) Gellhorn, E., Kessler, M., and Minatoya, H. Influence of Metrazol, Insulin Hypoglycemia and Electrically Induced Convulsions on Reestablishment of Inhibited Conditioned Reflexes, *Proc Soc Exper Biol & Med* **50** 260-262, 1942. (b) Gellhorn, E., and Minatoya, H. The Effect of Insulin Hypoglycemia on Conditioned Reflexes, *J Neurophysiol* **6** 161-171, 1943. (c) Kessler, M., and Gellhorn, E. The Effect of Electrically and Chemically Induced Convulsions on Conditioned Reflexes, *Am J Psychiat* **99** 687-691, 1943. (d) Gellhorn, E. Studies on Conditioned Reactions and Their Clinical Implications, *Journal-Lancet* **63** 307-312, 1943.

2 Gellhorn, E. Further Investigations on the Recovery of Inhibited Conditioned Reactions, *Proc Soc Exper Biol & Med* **59** 155-161, 1945.

positively established conditioned reaction resulting in suppression of a motor action would react differently to insulin coma than a negatively established conditioned reaction in which the animal likewise refrained from motor activity because the latter had been inhibited by lack of reinforcement, a new light would be thrown on the physiologic nature of the insulin effect

The main group of experiments, following a series of preliminary observations, was performed on 11 rats. In contrast to the apparatus used in the earlier work, which consisted of two chambers only, a circular apparatus divided into six chambers, was employed, which permitted the rats to escape from the shock into either of the two adjacent divisions. After the conditioned reaction was established, it was inhibited by lack of reinforcement, as in my earlier work. Then, insulin coma was applied, and the degree of recovery of the conditioned reaction was ascertained. This constituted the first part of the experiment (A). Thereafter the conditioned reaction was again fully established by reinforcing the conditioned stimulus. Then, this conditioned reaction was abolished, not by



Effect of insulin coma on the recovery of the conditioned escape reaction after this reaction has been abolished by internal inhibition (A) or by application of a countershock (B). The ordinate represents the percentage of recovery of the conditioned reaction (C R), the abscissa, the time, in days. The arrows indicate injection of insulin, leading to coma.

internal inhibition but by countershock, i.e., the electrical shock was applied to the grid of the two adjacent chambers when the conditioned stimulus was presented. The rat jumped, of course, into one of the adjacent compartments and was driven back through the shock into the original compartment. Repetition of this procedure for several days abolished the conditioned reaction completely. Thereafter insulin coma was applied in the same manner as in the first part of the experiment, and the degree of recovery of the conditioned reaction was again determined. This section of the experiment is referred to as part B. Then the rat was again retrained, i.e., the conditioned reaction was again established by reinforcing the conditioned stimulus with the electric shock, and part A of the experiment was repeated.

#### RESULTS

A typical experiment is shown in the graph. The periods of training during which the conditioned stimulus (a muffled bell) was reinforced by a slight electrical shock applied to the grid of the com-

partment and the subsequent periods of inhibition by lack of reenforcement are omitted in the presentation of part A of the experiment. Likewise, the establishment of the conditioned reaction and its abolishment by countershock are not recorded in part B of the graph. The record shows that when the conditioned reaction had been abolished by lack of reenforcement (A) the administration of insulin leading to coma induced the recovery of the conditioned reaction. If, however, the conditioned reaction had been eliminated by countershock, no significant recovery<sup>3</sup> of the conditioned reaction occurred. It is noteworthy that when part A was repeated in the experiment recorded in the graph two insulin comas were sufficient to cause a temporary recovery of the conditioned reaction of 100 per cent, so that the third coma could be omitted. The failure of insulin coma to produce recovery of the previously established positive conditioned reaction after countershock had been applied was obviously not due to a spontaneous change in

*Percentages of Recovery of Conditioned Reactions with Insulin Coma*

No	Percentages of Recovery		
	A*	B*	A*
30	50	10	30
37	50	30	50
7	50	20	50
55	50	10	
29	90	10	
52	50	20	
60		20	70
64	50	10	
36	50	20	50
31	80	20	

\* In column A fall the conditioned reactions inhibited by lack of reenforcement, in column B, those abolished by countershock.

the animal, since a repetition of part A after part B had been completed showed again the striking effects of recovery of an inhibited conditioned reaction induced with insulin coma. This result was confirmed in 10 more experiments, listed in the accompanying table in which it is also shown that the sequence of the two parts of the experiments (A and B, or B and A) is immaterial to the results. The recovery of the abolished conditioned reaction through insulin coma is possible only when this reaction has been eliminated by internal inhibition, and not when countershock is the cause of a new learning process leading to a new attitude (avoidance reaction) of the animal.

The clue to an understanding of the experiments just described seems to lie in the fact that the significance of the conditioned stimulus (bell), previously the signal for an escape reaction, was altered by its combination with the countershock. In these circumstances the escape

3 An increase of about 20 per cent was found to be insignificant in the experiments of Gellhorn and Minatoya.<sup>1b</sup>

reaction was suppressed and the behavior of the animals was overtly similar to that seen after internal inhibition. But important physiologic differences existed between these two situations. In the conditions present in part A of the experiment the temporary association between the conditioned reaction and the conditioned stimulus still existed, although in an ineffectual form, so that, owing to the lowered excitability of the brain as a whole as a result of internal inhibition,<sup>4</sup> the conditioned stimulus was unable to elicit the positive escape reaction (conditioned reaction). Under the influence of repeated insulin coma or similar procedures (electric shock and metrazol convulsions) these weak links between the conditioned stimulus and the unconditioned reactions are apparently intensified, and thus the original escape reaction reappears in response to the conditioned stimulus (bell). In the case, however, in which the conditioned reaction was abolished by countershock the situation is quite different, since a new positive conditioned reaction is substituted for the old one. The bell was the signal for an escape reaction during part A and the early portion of part B, but, whereas it retained this physiologic and symbolic significance in part A, although it lost its effectiveness, owing to lack of reinforcement, the bell became the signal for a new avoidance reaction in the crucial portion of part B. Since this reaction was established under the influence of a strong unconditioned stimulus (countershock), it replaced quickly the former conditioned reaction. The new behavior was easily acquired and apparently elicited a very stable conditioned reaction, in which the animal, on exposure to sound, refrained from escaping into the adjacent compartments. If the action of insulin coma and related procedures would produce an increase in the general level of excitability, it might cause an animal to react to the bell with a vigorous escape reaction in the two situations represented by parts A and B of the experiment, regardless of the fundamental difference in the nature of the physiologic reactions which form the basis of the behavior of the animal in the two parts of the experiment. The experimental results show clearly that this is not the case. The specificity with which insulin coma (and probably electrically induced convulsions) restores inhibited conditioned reactions without affecting the avoidance reaction established by countershock indicates clearly that these procedures act only on those cortical processes which, although latent during internal inhibition, are the basis of the conditioned reaction. This interpretation is in agreement with the observations in previous studies in which the effectiveness of insulin coma and electric shock in the restoration of inhibited conditioned reactions was directly related to

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4 The reader is reminded of Pavlov's demonstration of the relation of internal inhibition to sleep.

the stability of the conditioned reaction. Reactions to a bell, which were established with ease but abolished with difficulty, were more effectively restored with insulin coma or electric shock than were conditioned reactions to a light, which showed the opposite behavior, indicating a lesser degree of stability. On the other hand, the results of experiments reported in this, as well as in the preceding, paper seem to warrant the statement that positive conditioned reactions, no matter whether the conditioned reaction consists in a movement or in the suppression of a movement, are not altered by insulin coma.

Numerous studies have shown that the centers of the sympathetic system become more excitable as a result of insulin coma, electric shock and similar procedures.<sup>5</sup> Such effects may persist for considerable periods.<sup>6</sup> It must therefore be assumed that discharges from these centers, particularly from the hypothalamus, are increased above the normal value. Murphy and Gellhorn<sup>7</sup> showed recently that the sympathetic parts of the hypothalamus give rise to impulses afferent to the motor cortex, the primary sensory projection area and the association centers of the brain. These impulses increase the effectiveness of subthreshold stimulation of the motor cortex to such a degree that distinct movements may result. Furthermore, studies of the action potentials of the cortex have shown that under the influence of these hypothalamic impulses the cortical excitability is greatly increased and the number of active neurons enlarged.<sup>7</sup> These data suggest that cortical residues of previously established conditioned reactions may be activated as a result of the heightened hypothalamic activity following insulin coma. This may account for the restoration of inhibited conditioned reactions. That no generalized, nonspecific excitatory effects follow insulin coma is indicated by the fact that insulin coma becomes ineffective after suppression of the original conditioned reaction by the establishment of a new one (avoidance reaction).

To what extent these data are helpful in the interpretation of the mental changes characterizing psychoses for which "shock therapy" has been found to be of value, as well as in the understanding of the mechanism of recovery as the result of this form of therapy, remains to be determined by clinical investigators. However, the frequently recurrent statement in the clinical literature that nothing is known

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5 Gellhorn, E. *Autonomic Regulations*, New York, Interscience Publishers, Inc., 1943.

6 Gellhorn, E. *The Role of the Autonomic Nervous System in Problems of Rehabilitation*, *Federation Proc* **3** 266-271, 1944.

7 Murphy, J. P., and Gellhorn, E. *Hypothalamic Facilitation of the Motor Cortex*, *Proc Soc Exper Biol & Med* **58** 114-116, 1945, *The Influence of Hypothalamic Stimulation on Cortically Induced Movements and on Action Potentials of the Cortex*, *J Neurophysiol* **8** 341-364, 1945.

of the mechanism of the shock treatment is no longer warranted by facts in view of the extensive physiologic work regarding the action of insulin coma and related conditions on the central nervous system<sup>8</sup>

#### SUMMARY

A conditioned escape reaction inhibited through lack of reinforcement is restored by insulin coma and related procedures, as shown in previous studies. If, however, the escape reaction is abolished by countershock, i. e., by a shock applied to the adjacent compartments into which the rat escapes, treatment with insulin coma does not restore the escape reaction.

Although outwardly similar, the absence of the escape reaction in the two situations is based on dissimilar mechanisms. In the first situation a conditioned reaction disappears through lack of reinforcement, whereas in the second a new conditioned reaction is established by countershock. In agreement with a previous study, it is found that insulin coma acts only on inhibited conditioned reactions but does not influence positive conditioned reactions. The statement applies to the excitatory, as well as to the "inhibitory," type of the conditioned reaction.

It is suggested that the recovery of inhibited conditioned reactions with insulin coma is due to increased hypothalamic discharges to the cortex, which, according to investigations of Murphy and Gellhorn, may make subthreshold cortical processes supraliminal.

Miss Janet Bechtel assisted in this study.

University of Minnesota Medical School

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<sup>8</sup> Gellhorn,<sup>5</sup> chap. 19. The Autonomic Nervous System and Neuropsychiatry. Effects of Hypoglycemia and Anoxia and the Central Nervous System, Arch. Neurol. & Psychiat. **40** 125-146 (July) 1938.

## News and Comment

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### NEUROPSYCHIATRIC INSTITUTE AT THE MEDICAL COLLEGE OF ALABAMA

A neuropsychiatric institute has been created at the Medical College of Alabama and will be located in the school's teaching hospital, the Jefferson and Hillman hospitals, which will house on one floor the newly formed department of neurosurgery, neurology and psychiatry and all patients of the institute. Diagnostic, therapeutic, research and teaching services of the institute will be available to members of the medical profession at large.

This neuropsychiatric institute has been made possible by the Walter Haynes Foundation, which will subsidize study and research, in addition to the activities of the institute.

The staff of the institute is the same as that of the newly created department of neurology, neurosurgery and psychiatry. Walter G. Haynes, M.D., professor and chairman (neurosurgery), director of the Institute, Frank A. Kay, M.D., associate professor (psychiatry), Wilmot S. Littlejohn, M.D., associate professor (neurology), Donald Ramsdell, Ph.D., associate professor (psychology), Garber Galbraith, M.D., associate professor (neurosurgery), Samuel C. Little, M.D., assistant professor (neurology), William B. Patton, M.D., assistant professor (neurosurgery), Benjamin F. Morton, M.D., instructor (psychiatry), Stanley E. Graham, M.D., assistant, and William P. Tice, M.D., assistant.

### CONTRACTS BETWEEN VETERANS ADMINISTRATION AND PRIVATE MENTAL HYGIENE CLINICS

Inquiries have been received in the Department of Medicine and Surgery as to whether the Veterans Administration will cancel contracts with private mental hygiene clinics for the outpatient treatment of veterans when the Veterans Administration Mental Hygiene Clinics are organized and functioning. This has resulted in hesitancy on the part of some clinics to negotiate contracts.

In respect to these inquiries, it is the policy of the Veterans Administration to continue all such contracts indefinitely, provided the caliber of work justifies their continuation.

### AMERICAN PSYCHIATRIC ASSOCIATION

At the One Hundred and Second Annual Meeting of the American Psychiatric Association the following officers were elected: president, Dr. Samuel W. Hamilton, Washington, D.C., president-elect, Dr. Winfred Overholser, Washington, D.C., secretary-treasurer, Dr. Leo H. Bartemeier, General Motors Building, Detroit, Councillors: Dr. Kenneth Appel, Philadelphia, Dr. Karl M. Bowman, San Francisco, Dr. William C. Menninger, Topeka, Kan., and Dr. Thomas A. C. Rennie, New York.

### SOUTHERN PSYCHIATRIC ASSOCIATION

The Southern Psychiatric Association will hold its annual convention in Richmond, Va., on Oct. 7 and 8, 1946. The list of speakers will be furnished within the next sixty days.

# Abstracts from Current Literature

EDITED BY DR BERNARD J ALPERS

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## Physiology and Biochemistry

ELECTROENCEPHALOGRAPHIC STUDIES DURING FEVER INDUCED BY TYPHOID VACCINE AND MALARIA IN PATIENTS WITH NEUROSYPHILIS MILTON GREENBLATT and AUGUSTUS S ROSE, Am J M Sc **207** 512 (April) 1944

Greenblatt and Rose studied the brain wave patterns during the course of induced fever in 23 patients with neurosyphilis. Electroencephalographic tracings were obtained before the increase in temperature and at intervals of one-half to one hour during the fever. Observations on 54 paroxysms of fever were made, 34 of which were induced by injection of typhoid vaccine and 20 by malaria.

Before the fever the patterns of 8 of the patients were considered to be within normal limits, those of 5 were classed as borderline and those of 10 as abnormal. During the chill, the electroencephalogram showed evidence of pronounced muscular activity. The alterations in the tracing during the rise in temperature were (1) an increase in the irregularity of the pattern, (2) an increase in the number of slow, or delta, waves and (3) an increase in the voltage of the potentials. The rise in temperature was associated with progressive loss of the characteristics of the patient's basic electroencephalogram, and the pattern at a high temperature (104 to 105 F) was utterly different from that at the control temperature.

Several patients showed significant clinical changes during fever in the form of restlessness, irritability, listlessness and confusion. These patients showed the most striking changes in their electroencephalographic tracings. The main feature of the records was an increase in the slow, or delta, activity during fever.

It is believed that several influences, of which the metabolic rate is one, play a role in the alteration of the brain wave pattern during fever. The factors of temperature, metabolic rate, type of disease and type of induction of fever are considered as possible causal factors in the production of slow activity.

MICHAELS, M C, A U S

THE DISTRIBUTION OF DIPHOSPHOPYRIDINE NUCLEOTIDE IN THE BOVINE RETINA C B ANFINSEN, J Biol Chem **152** 279, 1944

Quantitative histochemical studies of frozen-dried sections of the retina indicate that the concentration of diphosphopyridine nucleotide varies considerably from layer to layer in this organ. The highest concentrations were found in the two synaptic regions. The layer of ganglion cells also contained considerable quantities of the co-enzyme. The rods and the outer nuclear layer, however, contained much smaller amounts. The results have been discussed with regard to the possible role of diphosphopyridine nucleotide in the transmission of the visual impulse through the mediation of acetylcholine.

PAGE, Cleveland

THE EFFECT OF GALVANIC EXERCISE ON DENERVATED AND RE-INNERVATED MUSCLES IN THE RABBIT E GUTMANN and L GUTMANN, J Neurol & Psychiat **7** 7 (Jan-April) 1944

In order to test the value of electrotherapy for peripheral nerve injury, the authors treated the muscles innervated by the peroneal nerve in a series of 30 rabbits. Galvanic current of about 4 to 6 milliamperes was used for about twenty minutes daily, and the results were compared with those for the untreated, opposite,



extremity The experiments were divided into two groups (1) treatment of denervated muscles without possibility of reinnervation and (2) treatment of muscles in which reinnervation was allowed It was found that in both groups electrotherapy with a strength of current sufficient to elicit vigorous contractions of the muscles delayed or diminished muscular atrophy, as confirmed by biopsy The most satisfactory results were obtained with a daily exercise of twenty to thirty minutes' duration The effect was greater after short term (thirty-seven days) than after long term denervation (sixty-seven to one hundred and fifty days), and in the latter situation the earlier the treatment was started after denervation the greater the effect Thus, after a maximal treatment beginning immediately after denervation the muscles lost only 17 per cent in weight in sixty days, as compared with a loss of 59 per cent in untreated muscles The time of onset of motor recovery following various methods of reinnervation was not appreciably affected by the galvanic exercise, although the degree of motor recovery was higher in the treated muscles

The results of these experiments showed that the effect of galvanic exercise varied with the time and duration of application of the current No harmful effect of fatigue in denervated muscles was found The effects of the treatment were still demonstrable four months after the galvanic exercise had been discontinued Since there was no significant difference in intensity of fibrillations between treated and untreated muscles, the authors are of the opinion that atrophy and fibrillations are independent processes

The observations suggest that activity is the leading factor in preventing muscular atrophy and that the impulses responsible for normal muscular activity which are lost after denervation can be effectively replaced by galvanic exercise This is probably brought about by increased metabolism in the denervated muscles through a better circulation

MALAMUD, San Francisco

### Psychiatry and Psychopathology

ELECTROENCEPHALOGRAPHY IN BEHAVIOR PROBLEM CHILDREN CHARLES I. SOLOMON, WARREN T. BROWN and MAX DEUTSCHER, *Am J Psychiat* **101** 51 (July) 1944

Solomon, Brown and Deutscher studied the electroencephalograms of two groups of 20 boys each, one group comprising the best behaved and the other the worst behaved in a school class The ages ranged from 13 to 16½ years The authors chose this age range to avoid correlations between age differences and the electroencephalogram, concluding that at the age of 13 years normal adult patterns are developed Social, economic and cultural backgrounds were similar for the two groups The authors found 12 abnormal electroencephalograms among the 20 best behaved children and 11 among the worst behaved children

The authors then studied in an institution for delinquent boys the electroencephalograms of the 10 least and the 10 most delinquent boys, finding abnormal patterns for 4 of the former and 9 of the latter There was no correlation of the electroencephalographic pattern and intelligence, efficiency of performance or personality

The highest incidence of abnormal electroencephalograms was found in the most poorly behaved institutional group, and thus the authors conclude may indicate a physiologic disturbance influencing behavior In view of the high incidence of abnormality found in normal children and the presence of normal and abnormal electroencephalograms among children presenting the same type of behavior problems, the authors conclude that it is difficult to interpret the significance of the electroencephalogram in an individual case The presence of abnormalities can be considered only as an additional, unfavorable personal factor

FORSTER, Philadelphia

SPEECH IN SENILITY FRED FELDMAN and D EWEN CAMERON, *Am J Psychiat* **101** 64 (July) 1944

Feldman and Cameron studied the speech of psychotic senile patients and compared it grammatically with that of normal adults and children. The most prominent difference between senile and normal subjects was displayed in the use of pronouns, verbs and adjectives. Senile persons used pronouns and verbs more frequently and adjectives less frequently. The use of pronouns was attributed to the tendency of such persons to repetitiousness and hesitancy. The diminished use of adjectives by senile persons may indicate the failing capacity to express themselves by the more complex mechanisms of speech. FORSTER, Philadelphia

PERSONALITY CHANGES CHARACTERIZING THE TRANSITION FROM CIVILIAN TO MILITARY LIFE GUSTAV BYCHOWSKI, *J Nerv & Ment Dis* **100** 289 (Sept) 1944

The transition from civilian to military life may, and often does, bring about personality changes in some persons. A number of mechanisms are responsible for the "preinduction anxiety" frequently seen. In some cases there is an abnormal fixation to the mother or to the wife, who represents a mother substitute. This is often rationalized as concern over her welfare. The fear of welfare of self is another frequent cause of preinduction anxiety. In men with a strong and insufficiently overcome castration complex this may take the form of fear of physical injury, while in others the threat of a potent and improperly integrated homosexual component may represent the real danger. A third important factor is the lack of integration into the superego of the ideals for which the war is supposed to be fought. In some persons the fear of induction represents a fear that repressed aggressive impulses may be released.

After induction the ego may be unable to establish new relationships because of a reactivation of old and unsatisfactory attachments to masculine members of the family. Frustration of excessive narcissism may lead to the development of a neurosis.

There are some personality types which fit well into military life. These are persons with a well integrated passive attitude or those in whom a sense of guilt has been satisfied by the subordination of personal activity to higher principles.

Some of the more obvious factors leading to nervous reactions in recruits are monotony, discipline, sexual deprivation, absence from home and the necessity for winning prestige in a new group.

The types of psychopathic reactions which occur vary widely and range from hypochondriasis and psychosomatic conversions to severe psychoses, usually of the paranoid variety.

CHODOFF, Langley Field, Va

THE EVALUATION OF PROGNOSTIC CRITERIA IN SCHIZOPHRENIA OTTO KANT, *J Nerv & Ment Dis* **100** 598 (Dec) 1944

Kant believes that the pessimistic view of some workers concerning the value of prognosis in cases of schizophrenia is unjustified and that when certain limiting conditions are taken into account a rather high degree of predictability can be obtained. The basis for prognostication is the clinical picture and its development. In general, the tendency toward persistence of uniformity of behavior and psychotic symptoms is a benign sign, while every trend toward discordance is a malignant sign because it refers to that basic disintegration of the personality which is the primary result of the schizophrenic process. An exception to this principle occurs when the disorganization is associated with clouding of consciousness, since it is then related to the temporary disturbance of the setting. Clinical structures which can be regarded as benign are (1) those in which clouding and confusion are persistent, (2) those in which the more schizophrenic-like symptoms, such as paranoid ideas and hallucinations, are centered around primary

changes in the emotional sphere of either a manic or a depressive character, (3) those in which alternating states of excitement and stupor are associated with fragmentation of mental activity provided that some of the characteristics of the malignant conditions which remain on a uniform psychologic level are not present

Of malignant import are all other conditions characterized by the predominance of "direct process symptoms," the latter term including both changes of behavior in the direction of disorganization, dulling and autism of gradual and insidious development, and the subjective perception on the part of the patient of a loss of normal feeling of personality activity and related experiences of foreign influence applied to mind or body

A prognostic indicator which may prove of value is the interview with the patient under the influence of sodium amytal. A schizophrenic disorganization which at least temporarily disappears under the action of the drug is less fixed than one which is resistant to the medication

An acute type of onset, a prepsychotic extraverted personality, pyknic body build and the presence of definite precipitating factors are indicative of a favorable prognosis

The author emphasizes that the value of prognostication is dependent on the accuracy of evaluation of the prognostic factors. Individual symptoms must be considered in relation to the entire picture

CHODOFF, Langley Field, Va

#### THE DUTY PROBLEM OF THE PSYCHIATRIC CASUALTY. A RAPID METHOD OF DECISION. ROBERT S. SCHWAB, War Med 6 144 (Sept) 1944

Schwab presents a simple neuropsychiatric evaluation sheet, which consists of a graph easily made out, to be attached to the psychiatric casualty's record, so that his condition and his prognosis can be understood at a glance. The graph has four variables: A. The amount of stress experienced by the patient, whether long hours of hard work in a tropical climate, intense danger under shelling and bombing, unusual responsibility, bad news from home or combinations of more than one factor; B. The degree or amount of the breakdown—including loss of ability to do work, loss of appetite, weight or sleep, fatigue, somatic symptoms, crying, amnesia, conversion symptoms, and any other significant facts; C. The amount of previous instability—abnormal personality traits, nervous breakdown, chronic illness, poor work, school or sex adjustments, bed wetting, overdependence on parents, and other inadequacies; D. The amount or degree of recovery or come-back after the stress has been removed by admission to the sick list and the start of therapy.

Analysis of the cases of men who fully recovered showed that their graph  $\frac{A \times D}{B \times C}$  was greater than 1. For those who retained their symptoms in spite of two months of therapy, the rate was less than 1.

PEARSON, Philadelphia

### Meninges and Blood Vessels

#### MENINGITIS DUE TO POST-TRAUMATIC CEREBROSPINAL RHINORRHEA. MILO C. SCHROEDER, Arch Otolaryng 40 206 (Sept) 1944

The most common cause of cerebrospinal rhinorrhea is trauma resulting in comminuted fracture. Other etiologic possibilities are (a) damage during an operation, (b) necrosis caused by pressure of a tumor or hydrocephalus, and (c) congenital anomalies. The bony defect may be found in the posterior wall of the frontal sinus, in the cribriform plate of the ethmoid bone or in the walls of the sphenoid sinus. The prognosis of cerebrospinal rhinorrhea is poor. Sooner or later meningitis develops.

Schroeder reports 2 cases of meningitis secondary to cerebrospinal rhinorrhea. In the first case a tumor of the cerebellopontile angle was removed through an

opening made in the skull behind the ear. Shortly after the operation the patient complained of a clear, salty fluid dripping from his nose. One month later meningitis developed, the predominating organism being the staphylococcus. In the second case cerebrospinal rhinorrhea developed two days after the patient had fractured his nose and face in a motor accident. On the third day after the accident unmistakable signs of meningitis were present. The offending organism was the pneumococcus. In both cases recovery followed heroic doses of sulfadiazine, adequate water intake and, in the second case, antipneumococcus serum, administered intravenously.

RYAN, Philadelphia

PREVENTION, TREATMENT AND END RESULTS OF MENINGITIS. N. SILVERTHORNE, *Canad M A J* **52** 252 (March) 1945

Silverthorne reviews 166 cases of influenzal meningitis and 271 cases of meningococcic infection (all bacteriologically proved) which were observed at the Hospital for Sick Children in Toronto between 1919 and 1944. The use of sulfonamide compounds has been the most important method of treatment in shortening the course and reducing the fatality. Influenzal meningitis has been sporadic in its occurrence. Meningococcic infections were sporadic until 1939, but from 1940 to 1943 there was an increase in the incidence of cases of this infection. Bacteriologically, 70 of the 71 spinal fluid strains examined from patients with influenzal meningitis have been of type B. Meningococcic infections during a sporadic occurrence of the disease have usually been caused by strains of type II. During an increase in the incidence of this infection in 1941 and 1942 there was a decided increase in the occurrence of strains of group I. Most patients with influenzal meningitis followed after recovery have been normal mentally and physically. All patients with meningococcic infection treated with sulfonamide compounds or with serum and sulfonamide compounds have been normal on discharge from the hospital.

J A M A

### Diseases of the Brain

POST-TRAUMATIC EPILEPSY. WILDER PENFIELD, *Am J Psychiat* **100** 750 (May) 1944

Penfield states that epileptic seizures may be produced by many types of injury to the brain. A closed injury seldom produces seizures, but when it does the injury usually produces a contusion, with subsequent scar formation. Subdural hematoma seldom produces chronic seizures except in the presence of a meningocerebral scar. With head injuries, penetration of the dura and laceration of the brain greatly increase the likelihood of seizures. Healed abscess of the brain results in a high incidence of chronic seizures. Simple meningitis seldom causes habitual seizures except when it results from thrombosis of cortical vessels, with subsequent scar formation. Cortical thrombophlebitis due to other factors is probably a frequent cause of habitual seizures. Epilepsy seldom follows cerebral embolism or thrombosis. Simple hydrocephalus rarely, if ever, produces chronic seizures. The types of focal cerebral injury here detailed may produce a focus of abnormal spontaneous neuronal discharge. Penfield, from his own observations, sees no importance in the inheritance of a tendency to fits. The focus of neuronal hyperirritability is not in the scar but in the adjacent cortex, usually a small marginal gyrus which has partially atrophied but contains functioning neurons. The vascular supply of such neurons is insufficient for constant adequate oxygenation. Therefore, in the surgical treatment of acute trauma any gyrus that is partially destroyed should be removed. In the surgical excision of epileptogenic scars such marginal partially atrophied gyrus must also be removed.

FORSTER, Philadelphia

INTRACRANIAL SUPPURATION SECONDARY TO DISEASE OF THE NASAL SEPTUM  
LLOYD K. ROSENVOLD, Arch Otolaryng 40 1 (July) 1944

Of the primary conditions that result in intracranial extension of infection, abscess of the nasal septum and submucous resection of the septum are probably the most common. Rosenvold reports 58 collected cases of intracranial suppuration secondary to septal disease. Though the incidence of complications is low, the mortality is high. There may be invasions of the intracranial space by adjacent, or regional, pathways and by distant, or indirect, pathways. The regional, or direct, extension comprises invasion (1) through traumatic dehiscences, (2) through natural bony passages, (3) through bony dehiscences consequent to osteomyelitis, (4) through veins by retrograde thrombophlebitis and (5) by way of the perineural sheaths of the olfactory nerves. The distant, or indirect, pathways are represented by (1) the general circulatory system (septic pathway) and (2) neighboring organs, with intermediate infection as a result of septal disease, e. g., otitis media following submucous resection. Extension to the intradural structures by way of the peripheral lymphatics probably does not occur. The author's experiments with rabbits seem to favor a vascular (thrombophlebitic) type of spread from the nasal septum to the intradural contents.

Of the various intracranial conditions consequent to disease of the nasal septum, purulent meningitis is by far the most common. Thrombosis of the cavernous sinus is next in order. Extradural and subdural abscess probably represent direct extension by osteitis or osteomyelitis. Abscess of the brain is rare.

Careful preoperative study is important in preventing complications following operation on the nose. Postoperative packing or splinting is a much disputed subject. Some surgeons never pack the nasal chambers after submucous resection, while others splint the septal flaps tightly. Tight and prolonged packing predisposes in many cases to postoperative suppurative complications by preventing free drainage. On the other hand, poor splinting may permit free bleeding, and the resulting blood clot may easily suppurate. The author believes that packing should never be left in the nose for more than twenty-four hours after an operation on the septum.

Acute tonsillitis following submucous resection is a complication that may favor intracranial extension of suppuration and should not be regarded lightly. The exact mechanism of extension in those cases in which otitis does not develop as an intermediate infection is not clear. To prevent tonsillitis, it is well not to keep the nose tightly packed for a long time. In cases in which both tonsillectomy and submucous resection are indicated, the former operation should precede the latter by several weeks.

RYAN, Philadelphia

MENIERE'S SYNDROME. RESULTS OF TREATMENT WITH NICOTINIC ACID IN THE VASOCONSTRICTOR GROUP. MILES ATKINSON, Arch Otolaryng 40 101 (Aug) 1944

Atkinson states that in cases of idiopathic Meniere syndrome one of two vascular mechanisms is at work. There may be a primary vasodilator or a primary vasoconstrictor mechanism, either of which can produce the characteristic picture. The two groups of cases can be differentiated by means of the intradermal test with histamine. Accurate grouping is extremely important because the treatment appropriate in one group is not only inappropriate but actually harmful in the other.

The series reported comprises 110 cases, in which treatment was given for the vasoconstrictor type of Meniere's disease over a three and one-half year period. Nicotinic acid was found to be the best drug for vasodilation. Its action is at the periphery of the vascular system, on the smallest vessels, as is evidenced by the cutaneous flush which follows its administration. This distal response is just the effect desired, since it is the circulation in the capillaries of the stria vascularis which is thought to be at fault, at least as far as aural manifestations are con-

cerned. It is essential to use nicotinic acid, and not nicotinamide. While the two drugs are interchangeable as regards their vitamin effect, they are not interchangeable as regards their vasodilator effect. Nicotinamide has no vasodilator action. The method of treatment found most efficacious has been to start with injections, intravenous or intramuscular, and then, after a period which depends on the response to treatment, gradually to wean the patient from injections to oral medication only. In this series of cases, in which treatment was exclusively with nicotinic acid, the vertigo was either relieved or greatly modified in 84 per cent.

RYAN, Philadelphia

THE NATURE OF TRANSIENT OUTBURSTS IN THE ELECTROENCEPHALOGRAM OF EPILEPTICS. DENIS WILLIAMS, *Brain* 67 10, 1944

Williams states that the electroencephalogram of epileptic patients during seizures is always abnormal, while the interseizure records may be either normal or abnormal. When abnormal, the record may be nonspecific, but an episode seizure discharge may be superimposed. Williams investigated the relation between the appearance of episodic discharges in the electroencephalogram and the liability of the patient to epileptic attacks. A patient who had had one definite and one questionable grand mal seizure was found to have spontaneous larval petit mal discharges. It was found that closure of the eyes produced similar electrical disturbances. During alterations in the  $pH$  and the gas tension of the blood the reflex disturbances behaved in the same way as to spontaneous wave and spike formations. The efficiency of the trigger mechanism, closure of the eyes, was not affected. Williams concluded that in this instance even the smallest paroxysmal outburst represented abnormal cerebral activity of an epileptic nature. The electroencephalograms of epileptic patients, normal controls, neurotic persons and patients with head injuries were studied and classified as normal or abnormal, and the abnormal records were further classified as (a) not specifically epileptic, (b) containing larval epileptic outbursts or (c) containing other paroxysmal outbursts. Larval epileptic outbursts included high voltage, abnormal waves with sudden onset and cessation, conforming to the described types of organized patterns. Other paroxysmal outbursts included all other types of transitory disturbances, such as are usually associated with epilepsy but are not well enough defined to be considered larval epileptic attacks. Williams found that abnormal electroencephalograms were six times as common in epileptic patients as in normal controls, larval epileptic disturbances occurred in more than 25 per cent of epileptic patients but did not occur in nonepileptic subjects, paroxysmal outbursts, both larval and others, occurred in 56 per cent of epileptic patients but in only 0.5 per cent of nonepileptic subjects, and paroxysmal outbursts occurred thirty times as frequently in patients with head injuries as in nonepileptic subjects and were more common after penetrating wounds.

Williams studied a group of patients with states frequently associated with epilepsy. This group was divided into patients with a constitutional and patients with a symptomatic epileptic tendency. Patients with a constitutional epileptic tendency included (a) twins both of whom presented paroxysms of wave and spike activity in their electroencephalograms, but only one of them had clinical seizures, and (b) a patient whose only seizure resulted from the oral administration of a small dose of camphor and who presented in his record paroxysmal disturbances suggestive of epilepsy. These disturbances were still present three and a half months after the administration of camphor and hence were considered indicative of a convulsive tendency.

Patients with a symptomatic epileptic tendency included (a) persons with paroxysmal outbursts without overt seizure (a patient with glioma of the right hemisphere, a patient with bilateral atrophy of the frontal lobe, a patient with osteomyelitis of the occipital bone and 3 patients with head injury) and (b) patients with paroxysmal outbursts following open or closed head injury and subsequently followed by overt seizures.

From these results, Williams concludes that the presence in the electroencephalogram of paroxysmal disturbances in an epileptic patient or in one suspected of having epilepsy can be confidently considered as supporting evidence for the diagnosis of epilepsy. Nonspecific and nonepisodic changes cannot be so construed. The presence of paroxysmal changes in the electroencephalogram in cases of known cerebral disease, for example, neurosyphilis, should not be considered as an argument against the validity of using the presence of such outbursts as confirmatory evidence of epilepsy when epilepsy is suspected but, instead, should be considered as evidence of a serious liability of the patient with cerebral disease to the development of epilepsy. Thus, the old clinical concept of latent and active epilepsy is supported by the correlation of clinical and electroencephalographic data.

FORSTER, Philadelphia

ACCIDENTAL HEAD INJURIES. PROGNOSIS IN SERVICE PATIENTS. C. P. SYMONDS and W. RITCHIE RUSSELL, *Lancet* 17 (Jan 2) 1943

This paper is concerned with a series of 242 service men with a variety of injuries to the head due to accidents which may also occur in civilian life, in contrast to head injuries sustained in actual warfare. The injuries are classified as "acute," signifying that the patients were admitted to the hospital within three weeks of the accident.

It is pointed out that post-traumatic amnesia ends when the patient is able to give a clear and consecutive account of the events around him. This lucidity must be continuous, and not punctuated by episodes of amnesia. A source of frequent error is the assumption that because a patient is aware of what is happening around him he will be able to recall these events later. Determination of the true end point of amnesia requires continuous, close observation. The duration of post-traumatic amnesia may be taken as an index of the severity of the injury only with limitations, namely, that it does not take into account the degree of local injury.

Comparison of the prognosis with the duration of the post-traumatic amnesia reveals that as the latter becomes longer the prognosis becomes worse. There is a rise in the proportion of deaths when the amnesia exceeds one day, and a further significant rise when it lasts over seven days. Of the group with the longer duration of amnesia, only one third returned to duty successfully. Among 193 of the patients who returned to duty, it was found that the incidence of relapse was not higher in those who had been treated for a relatively short period.

The study reveals that the prognosis is usually good. About 80 per cent of patients who survive the acute stage return to duty (usually heavy) within a few months. This figure is comparable to that pertinent to head injuries received in civilian life.

A resume of treatment follows. All patients were nursed in bed until they were free from symptoms and were then encouraged to get up and increase their activities gradually. The rate of progress was judged by the symptoms. Lumbar puncture was done in all cases but those of the mildest injury to ascertain the cerebrospinal fluid pressure and the presence or absence of blood. Puncture was repeated if the pressure was high (over 250 mm of water), if there was much blood or a considerable degree of pleocytosis and if the tap relieved headache or restlessness. Sufficient fluids were given to quench thirst. No restriction was placed on posture in bed. Sedatives were used as little as possible to avoid prolongation of mental confusion. Persistent moderate confusion was not considered a contraindication to the patient's being up provided he appeared none the worse for it. At times, naturally apprehensive patients were encouraged toward greater activity in spite of symptoms. Activity was not allowed to progress until headache, restlessness and excessive fatigue appeared. Gradually increasing activity was determined by the individual case.

Comparison of patients with acute injuries and a much larger group with chronic injuries (patients admitted more than three weeks after injury because

of unsatisfactory progress) reveals that the percentage of men returned to duty but invalided later was much higher in the latter group. The percentage of men finally invalided who had post-traumatic amnesia of over seven days was about the same for the group with acute injuries and for the group with chronic injuries. However, when the period of post-traumatic amnesia was shorter, the incidence of patients who were finally invalided was much higher in the group with chronic injuries. This indicates the presence of factors other than duration of post-traumatic amnesia which affect prognosis.

Symonds suggests that the mental constitution before injury plays an important part in the prognosis, hence, the predisposition to mental disorder was investigated in this series and was found to be more than twice as common in the group with chronic disorders. The investigation was based on the personal history, with respect to backwardness or failure to reach average standards at school, history of any functional nervous illness requiring medical care or absence from work, a poor work record, i. e., failure to hold a job longer than six months, or a family history of alcoholism, marked eccentricity, mental illness or nervous breakdown requiring medical care in the parents, sibs or blood relatives, such as uncles, aunts or step-siblings.

Comparison of the histories of all patients (acute and chronic) with evidence of this predisposition and the histories of patients who showed no such predisposition reveals that the percentage of the men finally invalided was nearly twice as high in the "predisposed" group.

Of 111 men with head injuries in the flying personnel of the Royal Air Force, only 13 (12 per cent) were invalided. These men had all been primarily selected by the air crew selection board as having a sound mental constitution. Of 844 men other than flying personnel, 405 (48 per cent) were finally invalided. Twenty (18 per cent) of the Royal Air Force group had a personal or family history of mental instability, as compared with 325 (38 per cent) of the group of 844 nonflying personnel. This relatively poor prognosis is not to be explained by less severe injury, as measured by the duration of post-traumatic amnesia, to the authors a relatively good mental constitution seems the most probable explanation of the difference.

SANDERS, Philadelphia

CHRONIC SOLID SUBDURAL HEMATOMA R. A. MONEY, M. J. Australia 1 224  
(March 3) 1945

According to Money, solid subdural hematoma is rare. A man aged 23 presented symptoms suggestive of the presence of a cerebellar tumor on the left side. Preparations were begun for an exploratory suboccipital operation. As a preliminary step, burr holes were made in the skull over both occipital lobes. On the left side the dura mater was thick and discolored, and when it was cut through brown fluid and old liquid blood escaped, indicating the presence of an old subdural hematoma. About an ounce (30 cc) of liquid was evacuated by lavage and suction, with immediate relief of symptoms, and a small piece of corrugated rubber was inserted in a forward direction. It was hoped that the remainder of the hematoma would drain out this way. After the discovery of the hematoma, the patient recollected that about the end of March 1942, while playing soccer, he had received a blow or kick on the head, which knocked him down. He continued the game for at least half an hour in a dazed condition, yet this minor injury must have been sufficient to tear one of the cerebral veins entering the sagittal sinus and start bleeding into the subdural space. Later the patient had a generalized epileptic seizure, the headaches persisted and papilledema increased. These, and other, observations made it obvious that a large, probably clotted and organized subdural hematoma was still present. After a large osteoplastic flap had been raised and the thickened dura reflected, a substance having the appearance of liver was encountered in all directions. This liver-like mass represented a solid subdural hematoma. The patient made a good recovery.

J. A. M. A.



## Diseases of the Spinal Cord

SECOND ATTACK OF POLIOMYELITIS AFTER THIRTEEN YEARS J WILLIE, *Canad J Pub Health* **36** 156 (April) 1945

A woman at the age of 32, in October 1942, had a second attack of poliomyelitis, having had a first attack thirteen years previously, at the age of 18. The first attack, which had developed after intimate contact with a sister who had a paralytic attack of poliomyelitis, had left the patient with wasting and flabbiness of the calf muscles of the right leg but with little loss of function. The patient walked with a slight limp. During the second attack, examination revealed a partial paralysis of both legs and weakness of the lumbar muscles. Wyllie reports that treatment with the Kenny packs was begun on the day of her admission to the hospital and was continued daily for twenty-five days. On her discharge there were some loss of power in the extensor muscles of the right thigh and loss of power in the muscles of the left thigh, but improvement in the muscles of the lumbar region.

J A M A

DELAYED PARAPLEGIA FOLLOWING FRACTURES OF VERTEBRAL L ROGERS, *Brit J Surg* **32** 514 (April) 1945

Rogers says that when paraplegia complicates a vertebral fracture it is usually a concomitant condition produced at once. Rarely is the onset of paraplegia delayed. He cites cases in which there was an interval between the injury to the back and the onset of paraplegia. A seaman aged 22 was blown up by a torpedo explosion, walked to the ship's side, clambered overboard, swam away from the ship and then became paraplegic. A member of the air force injured in a Spitfire crash experienced pain between the shoulders but no other symptoms. Paraplegia developed in forty-eight hours. Another patient had a cycling accident. He walked a mile, then sat down because of pain in the back and was unable to rise because of paraplegia. A girl of 17 was in a bicycle collision with a car. She picked herself up, was taken by car to the doctor's house and walked inside. She then experienced numbness and paralysis. In 2 of the described cases the paraplegia was transient, resolving completely in a few days' time. In the other 2 cases it was persistent, and exploration was carried out, with improvement in both cases following the removal of bony encroachment on the spinal canal. In the cases of transient paralysis delayed paraplegia is probably due either to subpial hemorrhage or to edema, which, when fully established at a varying interval after the injury, is sufficient to impair conduction in the cord. With absorption of the effusion in some twenty-four to forty-eight hours, or even longer, conduction is once more restored. Persistent delayed paraplegia is an indication for operation and removal of the bone block produced by displacement of the vertebral fragments.

J A M A

POLIOMYELITIS OF PSEUDOMYOPATHIC FORM M GESTEIRA, *Pediat e puericult, Bahia* **13** 117 (March-June) 1944

According to Gesteira, poliomyelitis of the pseudomyopathic type is characterized by sudden appearance of paralysis either after an infectious period typical for poliomyelitis or without such a period. Two or more members of the family become simultaneously ill, an occurrence which is rare with poliomyelitis. Early paralysis and consequent moderate atrophy are symmetric and are regularly distributed in the proximal areas of the limbs, near the pelvic and scapulohumeral joints. There is lordosis. The type of gait and posture is similar to that of myopathy. The hands become clawed or show a tendency to this deformity. In cases reported by the author the electrodiagnostic examination late in the course of the disease failed to show any reaction of degeneration, an observation which suggests complete regression of paralysis.

J A M A

CERVICAL DISK PROLAPSE B BROAGER, *Acta psychiat et neurol* **19** 45, 1944

In 5 of 285 cases of prolapse of an intervertebral disk the involved disk was in the cervical region. In 3 cases it was the sixth cervical intravertebral disk, in 1 case the fifth and in 1 case the fourth. Four of the patients were men, between the ages of 33 and 50, and 1 was a woman, aged 46. The history revealed traumatic injury to the spinal cord in 3 of the 5 cases. Pain was the most common initial symptom. In only 1 case was there quadriplegia, in 2 cases there were unilateral radicular paresis and atrophy, with inferior paraparesis in 1 of them, in 1 case there was inferior paraparesis only, and in 1 neurologic signs were normal. The Brown-Séquard syndrome was present in 1 case. Sphincter disturbances were present in 1 case. Roentgenographic examination revealed narrowing of the involved intravertebral space in 3 cases, in all 5 cases typical spondylosis deformans with osteophytes was demonstrated in the cervical portion of the spine, most pronounced at the level of the ruptured disk. Myelograms taken with iodized oil showed nothing characteristic of prolapse of the disk. A partial block was found in 2 cases and a total block in 2. The three distinct syndromes described by Stookey as typical of prolapse of the cervical disk may be useful if the differential diagnosis between a small prolapse of a cervical disk and intrinsic disease of the cord is difficult. But if the prolapse is large, the syndromes of Stookey will not be of any help in the differential diagnosis of intraspinal tumor and prolapse of a disk. The history of a specific traumatic injury to the cervical region of the spine combined with signs of an intraspinal tumor in this region should be suggestive of prolapse of a cervical disk. These symptoms, combined with roentgenographic signs of localized spondylosis deformans of the cervical region of the spine, especially narrowing of an intravertebral space, would also point to prolapse of the disk.

J A M A

# Society Transactions

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## ILLINOIS PSYCHIATRIC SOCIETY

David Slight, M B, *President, in the Chair*

*Regular Meeting, April 5, 1945*

### A Power Factor (P) in General Intelligence Effects of Lesions of the Brain DR WARD C HALSTEAD, Chicago

On the basis of work with patients with cerebral and other types of injury, with normal subjects and with infrahuman animals during the past ten years, I have formulated a set of behavioral indicators which have been validated biologically. An exploratory factor analysis was made of data relating to these indicators secured from 50 neuropsychiatric patients. The factor patterns were found to separate or to come together in biologically and clinically meaningful ways. One factor thus isolated has been identified as a kinetic power (P) factor. It is altered by injury to the brain, fatigue and anoxia and in certain psychiatric states (Halstead, *W J Psychol* 20 57-64, 1945, *Science* 101 615-616 [June 15] 1945).

During the early formative stages of personality in the growing child, it is probable that the power factor (P) operates to a greater or less extent as an antineurotic factor. In the normal adult its presence in adequate strength is a necessary protection against neurotic resolution of conflict. When the P factor is reduced by excessive physiologic stresses of military combat, for example, the consequence for the normal adult is the "combat neurosis," so commonly observed in the recent war.

Whether the P factor is similar to or identical with the concept of vigilance described clinically by Head as lowered in aphasic patients is not yet clear. While similarities are already suggested, direct comparison is hampered by Head's failure to specify quantitative indexes for the measurement of vigilance. More promising, however, is the prospect for comparison of the P factor with the general factor found by Lashley to be altered in proportion to the mass of lesions induced in the cortex of the rodent brain. Data on a diversified series of adequately studied patients, with histologic verification of their neural lesions, are necessary before this comparison can be made. My associates and I are slowly accumulating such data in our laboratory.

#### DISCUSSION

DR W S McCULLOCH, Chicago. I am happy to see a psychologic test that bears a rather fruitful relation to physiologic, or even anatomic, alterations. There are behind this short presentation so many kinds of data and so much of each kind that the simple conclusion, as the author stated it, can scarcely carry the weight that it should. The fascinating thing to me, a mere neurophysiologist, is this. The one effect to be expected from anoxia, the use of barbiturates, an inadequate blood sugar level or reduced temperature is a lowered metabolic rate of the nerve cells. Under such a condition the nerve cells would not be able to produce their normal potential in a normal length of time. It follows that if one tried to drive such nerve cells at high speed they would quickly fatigue, they would cease to respond. This would be detected most easily in the brain waves, which should be slow, and in the sensorium, which should be clouded, or in any demand for alternating performance, such as the flicker or the tapping test, or perhaps in the field of attention (I am not sure but that the problem of attention can be reduced to the same principle). At least this factor, of a physiologic nature,

is obviously an ingredient in the kinetic power of intelligence as it has been presented, for it is related to the repeated activity of nerve cells in the same way

The second condition that might easily underlie any diminution in the power factor is a lack of impulses coming in from other parts of the nervous system, and that would mean in general that, while plenty of attention might be left to handle a simple problem, there would scarcely be enough left for the whole peripheral field. There are within the central nervous system many reverberating circuits, which yield a background of excitation for the rest of the neural activity. Probably the largest single mass of such circuits runs through the frontal pole. Therefore, any large cortical injury, especially frontal lobotomy, by interrupting some of these circuits, should leave the patient with a fairly normal intelligence quotient but with inability to push through, probably a narrowing of the field of awareness spatially, and possibly temporally, the result should be social ineffectiveness. Thus, this second factor, of an anatomic nature, is to be expected as an ingredient of the power factor, for it also contributes to the repeated activity of nerve cells.

I like particularly the term "power factor," for it implies just what it should—a rate of doing work.

#### Group Therapy in an Extramural Clinic DR KATHARINE W WRIGHT, Evanston, Ill

Today, especial interest is being shown in group psychotherapy, owing to the fact that military psychiatrists have found it useful and beneficial. However, this method has other advantages, particularly for patients leaving mental hospitals.

Group therapy meets the need for treatment over a long period, it is consistent with the present psychologic studies, and it helps to desensitize and destigmatize, as well as to socialize, the patient.

The group therapy class at present under discussion is conducted for the purpose of helping hospital patients in their adjustment after return to home life, to teach them about their emotions and to instruct them how better to handle their emotions so as to cope with their present life situation. It is combined dynamics and reeducation.

The method used is as follows. The twenty-six letters of the alphabet are utilized as representative of twenty-six discrete, volitional acts, namely, the acts of writing the respective letters. The very simplicity and uniformity of these acts make them an ideal standard, safely within the usual levels of comprehension. How accurately and well the patient forms the letters is of little moment, it is the manner of his response which is important. This reaction of the patient affords specific diagnostic information to the therapist and frequently indicates the psychotherapy to be administered. For example, annoyance is frequently expressed at the extreme simplicity of the task. This usually indicates a concealed feeling of inferiority or inadequacy which troubles the patient. Or self-consciousness in varying degrees may be exhibited, thus suggesting emotional instability, such as is based on a sense of insecurity. Sullen resistance to the situation, indicating negativism, is sometimes encountered.

The therapist is often afforded the opportunity of administering effective treatment of these reactions on the spot. Usually this can be carried out by means of comments, made to the class and not to the patient, bearing on the nature of the patient's response, the probable causes of his maladjustment and the solution or cure, the parallel being always drawn between the patient's reaction to the test situation and his reaction to the situations presented in life.

This procedure may be varied in several ways. (1) The patients participating may proceed at their own speed and develop a group rhythm, (2) they may follow dictation, which puts them under an authoritative regimen, or (3) they may be confronted with a new situation, such as being asked to write with the left hand. In the first situation, many patients show inability to conform to the group activity and their annoyance at the incident restraint. Rebellion under

authority is a common reaction in the second situation, and in the third situation either fear or a decided relaxation of repression is usual

Within the last year there was developed the plan of taking notes of the day's proceedings, to be read and discussed at the next class hour. These notes serve as an additional educational tool. Special responsibilities are also assigned to certain members, such as keeping an attendance record and writing notices to absentees.

Statistical evaluations of any type of psychotherapy are difficult to make. However, data were secured with respect to attendance and diagnosis and comments from patients, visitors, doctors and nurses in answer to questionnaires sent out.

The following points were brought out from remarks made by patients. The patient learned to get on with other people, was helped to forget self, gained self confidence, became more independent in making decisions, learned how to relax, became more tolerant, gained an aim in life, learned the value of a goal, learned the difference between emotional reaction and intellectual judgment, enjoyed meeting friends. On the other hand, one woman resented the class after two years' attendance because it reminded her of the hospital. Class attendance was found to be a check on the degree of emotional stability.

It may be noted that most patients give a favorable response. The unfavorable response seems to come, for the most part, from persons with rigid personalities. Some of these persons do admit, however, that the friendly atmosphere in the class assists them to make better social contacts, and this must be considered as of at least some help. Also found in this group are patients who block themselves from help by their intellectual attitudes, nothing so simple could possibly help them. Regular attendance at class has modified this attitude. It is possible to get over to the patient that there is a considerable and important part of himself, other than his intellect, which greatly affects his life and well-being. Intellectual blocking is also found frequently among visitors, both professional and non-professional, it is hard for them to join in an emotional experience such as the class provides.

Comments from visitors were mostly favorable, especially from relatives of patients. Some of these visitors mentioned actual help to themselves and noted the benefit to the patients from the friendly atmosphere existing in the class. This bears out the comment of one of the physicians who visited the class, namely, that the important thing accomplished was getting the patients out of their pathetic isolation.

The therapeutic value of group therapy is now recognized by a large number in the psychiatric profession. It is a useful instrument in desensitizing a patient to his mental illness, it may serve to relieve him and his relatives of the stigma of hospitalization in a mental institution, and it affords an outlet for the socialization desperately needed by many neurotic patients and by psychotic patients whose condition has improved.

The studies in this field extending over three years corroborate several statements made by Dr. Paul Federn (Psychoanalysis of Psychoses, *Psychiat Quarterly* 17 470 [July] 1943). I agree with him that "it is not astonishing that most psychotics relapse at home or elsewhere when left without continuous support of transference." And, again, "one wins normal transference of the psychotic by sincerity, kindness and understanding."

In conclusion, it may be stated that the group treatment under discussion has met in a practical way the needs of many patients, approximately 240, leaving state hospitals. Not only does it afford the supportive therapy so urgently needed, but the nonverbal technic, a powerful emotional stimulant, provides at the same time a therapy which is both dynamic and educational.

#### DISCUSSION

DR. CHARLES F. READ, Elgin, Ill. This interesting communication follows a former article by Drs. Jacobson and Wright (*Psychiat Quarterly* 16 944 [Oct])

1942) Dr Wright has now applied this technic, as formerly described, to a group in an outpatient clinic. Complete understanding of her paper depends on knowledge of the former presentation, in which the technic was fully described.

This procedure is not a psychologic test in the ordinary sense of the term. It has not been standardized by comparison with the performance of so-called normal subjects. It is evidently a jointly subjective and objective attempt to evaluate the performance of patients observed along the lines she has indicated. As in any psychiatric examination, a great deal depends on the physician's evaluation of the patient in a more or less controlled situation.

For several years I listened to Dr Jacobson's discussion of this "test" as he developed it, and I must confess that not until I read the article in the *Psychiatric Quarterly* did I appreciate the various implications of the procedure. As described by the authors at that time, and again by Dr Wright in the present paper, it is evident that psychiatric insight can be obtained in this manner by one who is conversant with the technic—a method which, obviously, should be stereotyped in its application. Evidently, it cannot be picked up and applied offhand by any one and every one, now and then just as one pleases.

As suggested in the first article, many variations are possible if and when they may seem desirable. When one takes into consideration the development of the alphabet used in this procedure, one appreciates the fact that each letter is actually a picture derived through many, many changes during thousands of years. Somatopsychic coordination for the purpose of writing has been conditioned for years in educated persons. This "test" indicates cortical interference with these old patterns by reason of affective disturbances—disturbances such as occasion misbehavior of various sorts in other fields of neuromuscular activity.

It would be interesting, of course, to carry out this procedure under the hypnotic suggestion of such emotions as fear and hostility. Within its limitation, it parallels the psychic drama. In fact, the patient operating in this situation may well be described as enacting on a small stage a drama, with the psychiatrist standing by, not only as observer but as a participant in the play. The latter is accepted by the subject as a manifestation of his superego, as well as an aggravator of the handicapping forces with which he has to deal.

Doubtless, much of the good effect of this therapy results from group discussions, so well described by Dr Wright. The A B C's, used as described, seem to furnish an excellent basis for psychiatric guidance en masse, provided one can employ the technic with finesse.

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#### CHICAGO NEUROLOGICAL SOCIETY

Ralph C. Hamill, M.D., *President, in the Chair*

*Regular Meeting, April 10, 1945*

#### Diastematomyelia Report of a Case DR PAUL C. BUCY and DR HARRY P. MAXWELL

Diastematomyelia is a congenital separation of the lateral halves of the spinal cord.

A 9 month old child with a congenital dermal sinus at the level of the third lumbar vertebra was operated on for removal of the sinus, and an anomalous bony structure was found. Exploration revealed two separate spinal cords enclosed in one dura mater above the third lumbar vertebra and each cord descending caudally in its own dura mater below this level. The bony anomaly proved to be a spur projecting posteriorly from the body of the third lumbar vertebra and separating the two duras. At the age of 26 months neurologic examination revealed

a generally normal condition, with no gross evidence of spinal or cerebral dysfunction

A discussion of the literature included the summary of a review, in 1940, by Herrin and Edwards and a description of the anomaly studied in cross section, demonstrated in 1940 by Lichtenstein ("Spinal Dysraphism" *Spina Bifida and Myelodysplasia*, ARCH NEUROL & PSYCHIAT 44 792 [Oct] 1940)

#### DISCUSSION

DR A EARL WALKER I have seen 1 case of this anomaly (*Am J Roentgenol* 6 571-582, 1944) In that case there was a dilatation of the spinal canal at the site of diastematomyelia An operation was performed because I suspected a congenital tumor at that point, rather than splitting of the spinal cord I wonder whether there was such a dilatation in the case presented here

DR R P MACKAY May I ask where the surgeon found the conus terminalis, and how much of the cord existed below the spur of bone?

DR PAUL C BUCY We did not explore far enough down to find the conus, it extended into the lower lumbar part of the canal at least There was considerable anomaly of bone here, the spur shown in the drawing was not the only defect There was no spinous process at this level, and an anomalous development of the laminae existed There was, however, no definite enlargement of the spinal canal Roentgenographic visualization of the bony structure is not satisfactory in a child of this age I could not say that there was no dilatation at all, but none was detected

#### Angiomatous Malformation of the Sylvian Aqueduct with Remarks on Management of Aqueductal Obstructions DR CARL GRAF

This paper was published in full in the January 1946 issue of the *Journal of Neuropathology and Experimental Neurology*, page 43

#### Connections of the Cingulum DR WENDELL J S KRIEG

The cingulum has long been known to exist in man and the mammals generally It is usually considered to carry associational fibers of the medial, or cingular, cortex, and in man such connections certainly predominate Experimental lesions of the thalamus and cortex of the rat, however, demand a different interpretation of the cingulum

Fibers from the anterior nuclei of the thalamus enter the anterior thalamic peduncle and run as far forward as the rostral end of the caudate nucleus and then turn dorsally, perforating the corpus callosum, and form the rostral end of the cingulum Fibers reaching it at successively more caudal levels are piled on laterally Meanwhile, some fibers turn into the medial cortex There is a strong tendency for the axons to continue in the cingulum until they reach the caudomedial angle of the cortex, where they bend somewhat laterally and curve under the posterior forceps of the corpus callosum Here they terminate in the cortex of the retrosplenial region

The cingulum also receives representations from the ventrolateral thalamic nuclei These axons pass nearly directly laterally and dorsally and fall in place on the lateral aspect of the cingulum at a more caudal level than those of the anterior thalamic nuclei They do not show so strong a tendency to continue to the retrosplenial region but drop off along the way, both to the dorsal and to the medial cortex

The cingulum also receives representations from the cortex itself Each cortical lesion was shown to contribute to the bundle and its lateral extension by trails of granules, which became successively more oblique in the more caudal levels Many of these fibers do not reach the cingulum proper but, rather, enter a laminar lateral extension of it, immediately under the cortex

When reconstructed from the dorsal aspect, the cingulum and its accompanying lamina form a subcortical layer of regularly arranged, uncrossing fibers, which converge to the retrosplenial region There are no other accumulations of asso-

ciational fibers The direction of conduction seems to be exclusively caudomedial, not the reverse

Hence, in the rat the retrosplenial region is regarded as an important thalamic and cortical associational area A corollary of this is the principle that points in the cortex associate with other points caudomedially placed

#### DISCUSSION

DR G VON BONIN This paper is extremely valuable and has cleared up many points that were ambiguous The retrosplenial region is divided into a number of areas—26 and 29 are the most important It is not of the ordinary neocortical type However, in higher forms, as in primates, these areas shrink to insignificance and lie largely in the depth of the sulcus corporis callosi In our experiments on monkeys and chimpanzees, my associates and I have been able to establish connections passing from this retrosplenial area to the anterior nucleus of the thalamus We have not been able to find in monkeys any corticocortical connections, that does not mean that they do not exist They may not be massive enough to show up with the method we used, it may also be that the area is too small for the electrodes

Dr Krieg expressed doubt about the olfactory character of the hippocampus In view of the work of Fox and Magoun, I feel that the hippocampus should not be considered olfactory In an article in the ARCHIVES on the emotional mechanism, Papez proposed the association of the hippocampus with the anterior nucleus of the thalamus and the mamillary body I should like to ask Dr Krieg whether, on the basis of his experience, he has any comment on this concept

DR WFNDELL J S KRIEG Papez' ideas on the cingulum are very stimulating I do not know what I believe, except that it is the chief associational tract in the lower forms But it has been thrown into the limelight recently by the work of Freeman and his group, in Washington, D C, who say that in frontal lobectomy they can cut anything they like but that when they section the cingulum there are personality changes

I purposely hedged in my statements about this retrosplenial region, because I have not made the architectural study of the rat which I think is necessary At least, for my own purposes I want to know where the areas are It is certain that several areas in this region are much larger in the lower forms than in man There are other parts of the retrosplenial group which are strongly connected with the corpus callosum Thus, a major associational area is present here, but in higher forms I believe the emphasis has been shifted, perhaps it is the familiar situation of "paleo" and "neo" in associational mechanisms

#### The Mesodermal Tissue in Nerve Lesions and Repair DR FREDERICK HILIER

In one series of many hundreds of experiments on cats, the sciatic nerve was cut and sutured with black silk, or autogenous and homogenous grafts were employed to bridge gaps of 2 to 5 cm In another series, cats were shot through the thigh, and either nerve contusions resulted without interruption of the anatomic continuity of the nerve or the nerve was shattered Repair was effected in this group by end to end sutures or by grafts Histologic examination of all these nerves, by combining the Bodian and the Van Gieson stain, has revealed the importance of the reactions of the mesodermal tissue in the repair of nerve injuries

Milder forms of nerve contusion, like other forms of mechanical nerve trauma and so-called neuritis, lead to disintegration of the myelin sheaths with or without destruction of the axis-cylinders The original structure of the endoneurial tubes remains unaltered, and the nerve fibers regenerate within their old endoneurial sheaths The nerve fascicles retain their isomorphous structure, although the mesodermal endoneurium may react to the trauma with a localized cellular, and



later fibrous, hyperplasia, leading to some endoneurial fibrosis. The restitution of neural function is good and requires a short time.

More severe traumatic lesions of the nerve damage the mesodermal endoneurium as well. A histiocytic and fibroblastic proliferation ensues, which interrupts the continuity of the endoneurial tubes. As the mesodermal cells and fibers transgress the limits, the original endoneurium, the Schwann cells and the regenerating nerve fibers follow them. There are a profuse branching off, intermingling and confusion of young nerve fibers in the area of regeneration in such a traumatized nerve, and the isomorphous nerve structure is changed into a heteromorphous one.

When the trauma affects the border of the perineurium and the nerve fascicle proper, a mesodermal and ectodermal response follows, analogous to the reaction just described. As proliferating mesodermal elements of the endoneurium establish contact with the proliferating histiocytes and fibroblasts of the perineurium and epineurium, Schwann cells with regenerating nerve fibers leave the nerve fascicle and proceed between lamellas of collagenous fibers of the mesodermal perineurial membranes. They will grow in this new environment as far as the reactive mesodermal proliferation may attract Schwann cells.

The same guiding function of proliferating mesodermal cells in nerve regeneration is seen in every process of nerve repair. The ends of a divided nerve show the various stages of nerve trauma, increasing in severity toward the cut surface. Because of the caudal progress of neurotization, the relation of proliferating mesodermal endoneurial cells to Schwann cells and nerve fibers is more obvious in the central than in the distal segment. There is a gradual transition from isomorphous neurotization within intact endoneurial tubes, about 5 mm cephalad to the cut surface, to a more heteromorphous neurotization in the traumatized end of the central segment. The more gently a nerve is severed, the less will be the traumatic disorganization of the endoneurial tubes by mesodermal proliferation and the less the heteromorphous disarrangement of regenerating nerve fibers. When a nerve is not cut, but is severed by the shattering, bruising and tearing effect of a bullet, severe structural changes with heteromorphous neurotization within the fascicle and what may be called a herniation of ectodermal nerve tissue into the perineurium and epineurium are found several centimeters centrad to the nerve end. In the suture line itself, regeneration of nerve fibers by outgrowth of naked axons is negligible. The two ends are held together by mesodermal fibers, which assume in time the characteristics of collagenous connective tissue. It is along these fine mesodermal fibers, which can be stained for collagen a few days after injury, that the regeneration of nerve fibers in relation to proliferating Schwann cells gets under way. Schwann cells proliferate by themselves into the semiliquid medium of the nerve gap, but the main regeneration of fibers follows the scaffolding of the fibroblasts and their collagenous fibers. Strands of fibrin may act as guiding elements, but it seems most probable that here, again, the proliferation of mesodermal cells and fibers precedes the neurotization proper. Proliferating mesodermal cells and fibers, as well as Schwann cells originating from the distal segment, meet those from the central segment in the gap. Whatever the shape and direction of the mesodermal tissue elements between the separated nerve ends happens to be, it is this scaffolding which determines the course of the outgrowing nerve fibers into the degenerated distal segment. There is no need to assume that some sort of obscure chemotropism directs regenerating nerve fibers. The presence of such a hypothetic force is easily disproved by the usual deviation of regenerating nerve fibers which follow the proliferating fibroblasts of the hyperplastic perineurium and epineurium in the suture line. Nerve fibers accompanied with Schwann cells follow the proliferating mesodermal cells deep between the adherent muscle fibers, and a certain number almost regularly turn backward into the proliferative epineurium of the central segment and downward into the mesodermal sheaths of the distal segment. These fibers are lost to the ultimate functional regeneration.

In these experiments, a delayed end to end nerve suture—sixty days after the nerve was sectioned—produced a heteromorphous nerve structure over a greater distance and seemed to favor the undesirable deviation of regenerating nerve fibers into the excessively proliferative perineurium and epineurium of the central and distal segments

The study of nerve grafts affords a further illustration of this concept of neurotization. One has only to exchange the effect of a nerve trauma for that of a tissue necrosis to see that the process of neurotization remains practically the same. A freshly planted autogenous graft may heal, with the mesodermal endoneurial cells surviving this operation. The effect will be an isomorphous neurotization within the original endoneurial tubes, even though the habitual necrosis of the original Schwann cells results in a sort of *Abbau* of the decomposition products of the myelin sheaths and axis-cylinders, different from a wallerian degeneration. In an ideal case an autogenous graft may become neurotized, much like the degenerated distal segment of a sharply severed nerve.

Such ideal results are the exception with autogenous grafts and are never seen with homogenous grafts. Here, the neurotization is preceded by a mesodermal organization of the partly necrotic graft tissue. The original endoneurial membranes serve as a scaffolding for the proliferative mesodermal cells and seem to guarantee the maintenance of the direction of the mesodermal and, later, the nerve fibers. Yet the proliferation of the mesodermal cells and fibers is excessive, and far from being limited to the original endoneurial membranes. Wherever these membranes have succumbed to the general tissue necrosis, the mesodermal organization will become retarded and increasingly irregular. Finally, the mesodermal organization may include the perineurium and will then obliterate the anatomic and functional barrier between the perineurium and the nerve fascicle proper. The epineurium shows a conspicuous mesodermal proliferation. It is this kind of proliferative mesodermal organization which decides the neurotization of many autogenous and of all homogenous grafts. These grafts show a quantitatively good supply of regenerated nerve fibers, but their structure is heteromorphous, with an enormous amount of nerve fibers situated in many fine bundles between the dense collagenous fiber strands of the perineurium and epineurium. The nerve fascicles reveal an intense endoneurial fibrosis. One may say that the structure of a homogenous graft corresponds essentially to the neuromatous aspect of a severely traumatized nerve but appears to be more favorable than that of a suture line.

Our studies indicate that the use of dead tissue grafts or of grafts preserved in alcohol or other fixatives shows nothing but disadvantages. The necessary mesodermal organization is rendered much more difficult, and the irregularity of the final tissue structure is so great that a large percentage of regenerating nerve fibers never reach the distal nerve segment.

Nerve grafts in gunshot wounds show principally the same reaction as grafts used to repair a sharply sectioned nerve. There is frequently a more excessive mesodermal proliferation of the epineurium, with epineurial neurotization of the graft, depending on the interval after injury at which the transplantation has been performed. The often difficult mesodermal organization of grafts requires considerable more time for the functional regeneration of a nerve than does an end to end suture. The final effect may suffer from extensive, thorough necrosis of the graft, as well as from the intense fibrosis within the graft.

#### DISCUSSION

DR GEORGE B. HASSIN. In 1907 Perroncito, a brilliant student of problems of nerve degeneration and regeneration, gave in one of his contributions 700 references—probably more, as I got tired counting them. Since then the number of contributions has increased considerably, and, as Dr Hiller has shown in his exceptionally good demonstration, the interest in this subject is still alive. I can touch only on some points brought out by Dr Hiller, by showing five lantern

slides My experience with the pathology of nerve injuries is based on the study of 32 cases from Spielmeyer's collection of 180 cases, all from World War I. The nerves from each case had been sectioned and stained with four methods and thus were ready for investigative work. In addition, I studied the rich experimental material of Nageotte (Paris) and Ranson.

It seems that the behavior of the mesodermal tissue in nerve degeneration and regeneration depends on the type and the severity of the injury. With mild forms, when the nerve fiber has been cut, the myelin, axon and adjacent membrane and cells of Schwann degenerate below the place of injury and, as a diagram of Hjelt's (1860) shows, only the endoneurial, mesodermal membrane remains in the peripheral stump. Into the empty tubes formed by the parallel rows of the endoneurial cells grow new nerve fibers from the central stump. Hjelt assumed that the preserved endoneurial cells become transformed into nerve fibers. Such a view is, of course, inadmissible, as mesodermal tissue cannot be transformed into nerve fibers. Thirty-one years after Hjelt's publication, Bungner described in the peripheral stump parallel rows of fibers and nuclei known as cell *cordons* of Bungner, who stated that they consisted of cells of Schwann. The cells became, he thought, "neurotized", that is, they were transformed into nerve fibers and fused with the central stump, and thus a regenerated nerve fiber was formed. Bungner's conclusions, like those of Hjelt, were not based on facts, as his cell *cordons* are not formations of Schwann cells but rows of endoneurial cells, to which Dr. Hiller has repeatedly called our attention.

The behavior of the mesodermal tissue is different with severe injuries, such as lacerations of nerve fibers. The proliferation of the connective tissue fibers is not in the form of isomorphous strands, as Dr. Hiller called them, but of irregularly scattered masses, forming scars, which prevent any possibility of nerve regeneration. With a third type—mild contusion or concussion—there is no mesodermal reaction whatever, both the parenchyma and mesodermal tissue undergoing necrosis. On the whole, the results of Dr. Hiller's excellent experimental studies (on cats) wholly coincide with observations on human subjects, demonstrating the great importance of the mesodermal tissue in injuries of the peripheral nerves, in the processes of their degeneration and regeneration.

DR. FREDRICK HILLER. I wish to emphasize the point that in my opinion the different nerve elements react as a unit, in degeneration and in regeneration. The proliferation of the endoneurial, mesodermal elements is an essential part in nerve regeneration and determines the character of nerve regeneration, particularly in cases of nerve injuries. My studies on many hundreds of different nerve injuries and nerve grafts have shown how the neurotization of nerve sutures, of nerve contusions and of various grafts follows the pattern of primary mesodermal organization. The observations, as demonstrated in the pictures shown here, could never have been made by examining human material only. I feel that the role of the mesodermal tissue in nerve regeneration has been neglected heretofore and that new concepts have been developed which will lead to a better understanding of this process.

## Book Reviews

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**Intelligence and Its Deviations** By Mandel Sherman, M D, Ph D Pp 286, with illustrations, glossary and index New York The Ronald Press Company, 1945

In the first sentence of his preface the author states that "the purpose of this work is to present theoretical, experimental and clinical material on intelligence and its deviations. The subject is presented in such a way that it may be used in courses in departments of psychology and medicine." He proceeds to do this by gathering together in one volume of fifteen chapters the material usually found in books on general, social and abnormal psychology. The orientation is primarily that of the academic psychologist and the physician. There is considerable discussion of theoretic questions, such as a definition of intelligence, mental growth and the relation of environment and intelligence. There is some mention of less frequently recognized, but nevertheless important, problems connected with the measurement of intelligence. Thus, the question of motivation is touched on, as well as the difficulty of establishing a zero point in the measurement of intelligence and the frequently found disparity between intelligence and the level of the adjustment. On the whole, however, the author adheres to the more usual aspects of intelligence and intelligence testing. The facts are stated in simple fashion and are often supported with experimental data.

The weakness of the book, and it is a serious one, lies in the fact that the author makes no mention of the new approaches in intelligence testing. He still lays most of his emphasis on problems of mental classification and questions of deficiency, at least four chapters being devoted to various aspects of mental deficiency. While this discussion may be of value to the medical student, mentioned in the preface, it does not merit so much importance in a book on intelligence, especially when newer and more important aspects of intelligence testing are neglected. The psychologist who administers the intelligence test has long moved on from the approach which concerned itself primarily with mental level alone. Nowhere in the book is mention made of the psychologic research which evaluates the deviations in mental functioning in order to obtain an objective personality picture, a measure of mental deterioration and, in some instances, a diagnosis of mental disease. Rather, the author says that it is difficult to define the "exact mental level of a psychotic patient because the raw score on a test cannot give information as to the deteriorative process." Although he points out that certain failings are likely to occur with certain types of mental illness, he does not recognize the value of such clues but, rather, brands the tests as inadequate. In general the book must be considered relatively superficial and as adding little to the understanding of intelligence and its deviations.

**An Introduction to Physical Anthropology.** By M F Ashley Montagu, Associate Professor of Anatomy, Hahnemann Medical College, Philadelphia Price, \$4 Pp 326 Springfield, Ill Charles C Thomas, Publisher, 1945

This book is an excellent introduction to a complex and controversial field of scientific investigation. The author presents his material in a clear, concise manner, and without bias. It is intended for the general reader rather than for the specialist and covers a great deal of ground.

In a brief introduction, the author defines the scope of physical anthropology. He then describes seriatim the zoologic classification of the primates and discusses the factual basis for the theory of man's origin and evolution from an anthropoid progenitor. Considerable space is devoted to an analysis of the divisions and ethnic groups of man, with emphasis on the difficulties encountered by anthropologists in

developing sound criteria for classification. The last part of the book deals with the subtle relationships of culture, mind and body and the much disputed question of the relative importance of heredity and environment on man's development. At the close of each chapter there is a selected list for further reading. The accepted methods of measurements in physical anthropology are listed and described in the appendix. The index is unusually complete and contains numerous cross references.

Prof. Ashley Montagu, in agreement with most eminent anthropologists, is a firm believer in the fundamental spiritual and biologic equality of all mankind. Throughout the book he intersperses pithy comments, supported by scientific facts, on the absurdity of the concept of "race and blood superiority" and points out that "cultural isolates" do not represent genetically discrete "races," as is often assumed by the uninformed layman. An interesting section of the book reviews the evidence that the physical characteristics of a "pure race" actually change when the group is transplanted to a new physical environment.

Of particular interest to students, scientists and educators this book is highly recommended as instructive and interesting reading.

**Examining for Aphasia. A Manual for the Examination of Aphasia and Related Disturbances.** By Jon Eisenson. Pp. 28, with 4 pages of illustrations. New York: Psychological Corporation, 1946.

This manual has been compiled by a clinical psychologist and speech pathologist and is intended for the use of speech pathologists in planning a program of language rehabilitation for individual aphasic patients. The manual presents a comprehensive language examination in a clear form and should be useful for recording the progress in language function. The instructions for the various test items are specific and easily followed, and much of the test material is included in the manual.

The author states that his interest is in speech therapy, and not in neurologic and neurosurgical implications of language dysfunctions; consequently, it is not a criticism of his work to point out that the examination is not entirely satisfactory for use by the clinical neurologist.

## PRETRAUMATIC PERSONALITY AND PSYCHIATRIC SEQUELAE OF HEAD INJURY

### II Correlation of Multiple, Specific Factors in the Pretraumatic Personality and Psychiatric Reaction to Head Injury, Based on Analysis of One Hundred and One Cases

HARRY L KOZOL, M D  
BOSTON

THIS paper is a study of the relationship between multiple specific factors in the pretraumatic personality and the psychiatric sequelae of head injury

In part I<sup>1</sup> of the study I presented the results of a correlation of the categorical pretraumatic personality and the general psychiatric reaction to head injury of 200 patients. Each patient in that series had been given a categorical classification of the pretraumatic personality under one of the following ten headings

- Normal personality
- Psychopathic personality
- Neurotic personality
- Personality variant
- Normal personality except for general nervousness
- Mental deficiency
- Neurotic traits in childhood
- Behavior problem (childhood and youth)
- Psychotic behavior
- Pretraumatic personality unknown

Comprehensive personality classification is common practice in psychiatry, as in general medicine and neurology. It was recognized,

From the Neurological Unit of the Boston City Hospital and the Department of Neurology, Harvard Medical School

The work described in this paper was initiated under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the President and Fellows of Harvard College. It was completed subsequent to the termination of the contract.

1 Kozol, H L. Pretraumatic Personality and Psychiatric Sequelae of Head Injury. I. Categorical Pretraumatic Personality Status Correlated with General Psychiatric Reaction to Head Injury Based on Analysis of Two Hundred Cases, *Arch Neurol & Psychiat* 53:358-364 (May) 1945

however, that such a general personality classification might be inadequate in contributing information regarding the etiologic factors in the psychiatric sequelae of head injury. In part I<sup>1</sup> the pretraumatic personality types were correlated with the following post-traumatic psychiatric phenomena:

- Anxiety states
- Fatigue (neurasthenia syndrome)
- General nervousness
- Hypochondriasis
- Obsessive-compulsive-phobic states
- Depressive states
- Euphoria

It was found that 64 out of the 200 patients showed one or more of these symptoms, each of which had been explicitly defined in keeping with general psychiatric usage.

It was concluded

there is little, or no, correlation between [categorical] pretraumatic personality and the liability to development of post-traumatic mental symptoms. A patient with a pretraumatic "neurotic" personality may be free from symptoms. A patient with a pretraumatic "normal" personality may be crippled by mental symptoms. This does not mean that the pretraumatic personality may not play a large, or even the sole, part in the production of post-traumatic mental symptoms. It does mean that the development of post-traumatic mental symptoms may not generally be ascribed to the pretraumatic personality. There is no general rule that patients with over-all neurotic or psychopathic personalities are more likely to manifest symptoms after trauma than are normal persons.

It was further concluded that there is "a significant correlation between the incidence of post-traumatic mental symptoms and the existence of complicating psychosocial factors," such as the persistence of associated bodily injuries, occupational stresses, marital difficulties and pending litigation or continuing compensation.

In the present study, which dealt with every other patient in the previous study, a more intensive investigation was made of multiple, specific factors in the personality, both before and after head injury. It was recognized that categorical classification might overlook factors which might be present in various personality groups. It was felt, furthermore, that the number of post-traumatic psychiatric phenomena dealt with in the previous study might be inadequate in giving a picture of the psychiatric reaction to head injury. The observations in the present study are also correlated with categorical personality classifications. Finally, this study embraces correlations with the nature and severity of the head injury, as such, and the existence of complicating psychosocial factors, in an attempt to elucidate the psychiatric sequelae of head injury.

## MATERIAL

The 101 patients on whom this study was based represent approximately one half of a group of 200 subjects of a comprehensive investigation of civilian head injuries conducted at the Boston City Hospital from July 1942 to October 1944, under the direction of Dr D Denny-Brown, who has already presented a summary of the results of that study<sup>2</sup> These patients had been selected from a series of 430 persons with acute head injuries who had been admitted to the hospital immediately after injury, by exclusion of persons under 15 and over 55 years of age and of vagrants, irresponsible and unemployed alcohol addicts, chronically unemployed persons and patients on whom follow-up studies were unobtainable In the present study, 2 patients with chronic alcoholism were included because of the gross severity of their head injuries and the fact that they had histories of some work dependability Of the 101 patients in this study, 66 were males and 35 were females Eight patients were between 15 and 20 years of age, 26 were between 20 and 29, 20 were between 30 and 39, 31 were between 40 and 49, 12 were between 50 and 55, and 4 were over 55 Seventy per cent of the patients were under the age of 46 With but few exceptions, these patients had been selected at random in that every other patient admitted was selected for the present study, in addition to the regular study described in part I The minimal period of observation was six months unless the patient showed freedom from symptoms previous thereto Approximately 20 per cent of these patients were followed for more than one year, and some have been followed longer Each patient underwent at least three detailed examinations after discharge from the hospital The examinations took place at intervals of six weeks, three months and six months after discharge but in some instances were more frequent and in some cases were continued up to nine and twelve months after discharge

## METHOD

In order to evaluate psychologic factors in sequelae to head injury, one must have a base line That base line is the pretraumatic personality By reference to the pretraumatic personality one can determine whether there has been a change since the head injury

The necessity of establishing a personality base line resulted in my adherence to the historical-biographic method of personality study I wished to know what sort of a person the patient was before he had been injured It was obvious that a history of the patient's actual performances and experiences in certain situations would provide the most dependable basis for judgment This is the classic psychiatric case history This method is open to various criticisms It goes without saying that the history may not cover enough ground or be sufficiently penetrating It was sought to make the histories as accurate as possible by checking the initial history at subsequent examinations of the patient, by interviews with relatives and by information obtained from various other sources by a social worker This method of getting information about the patient's personality is tedious and time consuming A short cut would have been welcomed, but in the present state of knowledge of human nature I know of no adequate substitute for a painstaking, detailed history of the patient's "past performances and experiences in their special settings"<sup>1</sup>

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<sup>2</sup> Denny-Brown, D Disability Arising from Closed Head Injury, *J A M A* 127 429-436 (Feb 24) 1945



As none of these patients had ever been given any formal personality tests, such as the Minnesota or the Rohrschach test, before the head injury, there was no logic in giving such tests after the injury because there was no basis for comparison. With what could a patient's post-traumatic reaction to ink blots be compared?

In general psychiatric history recording, information which has been obtained in the course of prolonged interviews with patients is often lost in the lengthy descriptions and reports of the conversations. To get around that, a master work sheet was devised. This work sheet includes a list of 60 items, most of which are descriptive of personality traits, tendencies or characteristics. The full list follows:

Work record unsteady	Emotional instability
Steady, few jobs	Emotional incontinence
Steady, many jobs	Impulsiveness
Alcoholism	Fatigability
At time of injury	Apathy
Chronic	Abulia
Periodic	Obsessive-compulsive-
Asocial attitude (delinquent,	phobic state
criminal)	Hypochondriasis
Timorousness	Anxiety, chronic
Prudence	Anxiety attacks
Recklessness	Anxiety
Aggressiveness	re head
Ambitiousness	re family
Responsibility	re occupation
Irresponsibility	re other matters
Gaiety	Hysteria (conversion
Euphoria	dissociation)
Seriousness	Sex disturbances
Depressive state	Insomnia
Gregariousness	Fitful sleep
Seclusiveness	Increased need of sleep
Egocentricity	Nightmares
Introspectiveness	Dreams (of accident)
Altrocentricity	Difficulties in concentration
Extrospectiveness	and memory
Sensitiveness	Headache
"Schizoid" attitude	Steady
Restlessness	Periodic
Tenseness	Dizziness
Irritability	Vertigo
Excitability	Palpitation
Emotional stability	Hyperhidrosis
	Gastrointestinal disturbances

This list of items was selected arbitrarily by me. No claim is made that it encompasses every possible trait or deviation of personality. "Personality" is the sum total of one's tendencies, trends, capacities, liabilities, sensitivities and modes of reaction. Obviously, a complete list of all such possibilities would be nearly interminable and would, in fact, exceed any available vocabulary. In the interests of practicality, therefore, the list had to be rather arbitrarily limited. On

the basis of my experience, it appeared to me that the list selected was adequate and workable and that it embraced a sufficient number of significant items. The object of the use of this list was to provide a series of subjects for the uniform and controlled psychiatric examinations of these patients. The patients in this study came from all walks of life but mainly from the laboring, and even less privileged, classes. Some were earnest, steady citizens, others were indolent, alcoholic, irresponsible and even criminal. No rigid test could have been uniformly applicable to such a heterogeneous group which included persons of both sexes and of ages from 15 to 55 years (and beyond). With the use of a list of items as a guide, all patients were given substantially the same examination. Each item was used as the basis of special questions, each tailored to the particular background of the patient under examination. No arbitrary set of questions could have been generally applicable to this group of patients. It was necessary to adapt the examination to the patient.

It is thus obvious that this examination was not of the check sheet type. Despite the fact that patients were graded with respect to the strength of these items, all judgments were based on classic clinical psychiatric investigations. The list was simply a schema for uniformity of examination and recording in order to encompass a representative collection of traits, tendencies, characteristics, foibles, symptoms and complaints.

It will be noted that the list contains some items which may not ordinarily be included in considerations of personality. Thus, the first three items in the list refer to the patient's work habits. It must be conceded that consideration of such items offers considerable objectivity concerning the subject's makeup. The next three items deal with questions of alcoholism. The principal criticisms may be leveled against the inclusion of the last seven items in the list. These concern the presence of headaches, whether steady or periodic, and of dizziness, vertigo, palpitation, hyperhidrosis and gastrointestinal disturbances. They were included because, as they are common sequelae of head injury, it was deemed important to ascertain whether they existed before head injury. A further reason for including them was that this entire list was used as a schema for post-traumatic definition of the personality status. It appeared desirable, therefore, to include these items of a somatic class in order to avoid any assumptions as to whether they were due to organic lesions of the brain as such or were psychologic reactions to the trauma.

Most of the items in the list are familiar to psychiatrists. While it was desirable to avoid using words or terms which tended to beg questions by appearing too finalistic or diagnostic, it appeared desirable to include such terms as "schizoid," "obsessive," "compulsive," "hysterical" and "hypochondriacal." These terms were used not to indicate syndromes but, rather, to denote types of symptoms. Thus, "schizoid" does not indicate schizophrenia but, rather, designates oddity of personality in the sense of detachment from warm social rapport. The patient's attitude toward society and other persons appeared particularly relevant, as were also matters relating to his emotional balance and, particularly, his susceptibility to states of anxiety. The last item was considered under various subdivisions. Thus, a distinction was made between the occurrence of circumscribed attacks of anxiety and chronic states of anxiety. In addition, specific anxiety relating to the head was included because of Schilder's statement that such concern played a large part in the genesis of post-traumatic neurotic states.<sup>3</sup>

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3 Schilder, P. *Neuroses Following Head and Brain Injuries*, in Brock, S. *Injuries of Skull, Brain and Spinal Cord*, Baltimore, William Wood & Company, 1940.

Psychopathy and normality are not mutually exclusive, they involve quantitative, as well as qualitative, factors. On the basis of such a premise, each item in the list of traits was quantitated clinically on a scale of 0 to 3. Where possible, quantitation is always desirable. However, the accuracy of quantitation is often limited by the nature of the subject matter. It was felt that quantitation on a simple scale of 0 to 3 would be in closer accord with the possibility of clinical psychiatric evaluation than quantitation on a more elaborate scale. If, in my opinion, a particular trait was absent, the item was graded as 0. If present in minimal degree, the trait was graded as 1, if present in moderate degree, it was graded as 2, if present in maximal degree, it was graded as 3. It is submitted that such clinical quantitation or approximation of the strength of a particular trait or factor is certainly more accurate and desirable than gross categorization of a total personality. This multidimensional system made it possible to keep in constant perspective a large number of specific judgments. It is recognized that no such schema can do justice to the subtle interplay and reciprocal participation of those features of the personality which usually present an integrate of behavior. Yet it was felt that specification was desirable, if only to test the potentialities of such a method.

The work sheet of a particular patient is presented here (table 1). It will be noted that the 60 items are arranged in two columns, of 30 each. To the right of these there are several ruled columns. In the first such column, labeled "pretraumatic rating," the estimated pretraumatic value for each specific trait was placed. The columns beyond were used for listing the valuation of each trait at specific intervals after discharge from the hospital. Thus, a running quantitative assay of the post-traumatic personality was made. This then provided data concerning what changes, if any, took place with respect to each trait in the list. Thus, for instance, it may be noted that, whereas the patient was neither gay nor euphoric in his pretraumatic state, he was extremely so (with a value of 3) two months after his discharge from the hospital and moderately so (with a value of 2) six months after discharge. Other changes may be noted.

This work sheet also included information regarding other matters such as the patient's age, sex, dates of admission to and discharge from the hospital, the duration of unconsciousness, disorientation and amnesia and such clinical conditions as skull fracture and blood in the cerebrospinal fluid. It also included data concerning various complicating psychosocial factors, date of return to work, a categorical personality diagnosis, an estimate of the severity of the injury to the brain and of the associated bodily injuries, if any, and an estimate of the severity of the sequelae, as limited by the list of 60 items. It also provided for information concerning the family history, the personal psychiatric history and whether there had been any disproportionate

TABLE 1—Sample Work Sheet for Personality Study

Scale 0 3	Pre traumatic Rating of Each Trait	Post Traumatic Ratings					Scale 0 3	Pre traumatic Rating of Each Trait	Post Traumatic Ratings				
		Date		Date					Date		Date		
		9/14	11/30	3/2	6 Mo	9 Mo			9/14	11/30	3/2	6 Mo	9 Mo
Work	1						Emotional Status	2	1	1	1	1	1
Unsteady	0						Stable	1	2	2	2	2	1
Steady, few jobs	2						Unstable	0	0	0	0	0	0
Steady, many jobs							Incontinent	1	1	1	1	1	1
Alcoholism	1						Impulsiveness	0	0	0	0	0	0
Time of injury	2						Fatigability	0	0	0	0	0	0
Chronic	2						Apathy	0	0	0	0	0	0
Periodic	2						Abulia	0	0	0	0	0	0
Asocial tendency	0	0	0	0	0	0	Obsessive compulsive states	0	0	0	0	0	0
Timorousness	0	0	0	0	0	0	Hypochondriasis	0	0	0	0	0	0
Prudence	1	1	1	1	1	1	Anxiety, chronic	0	0	0	0	0	0
Recklessness	1	1	1	1	1	1	Anxiety attacks	0	0	0	0	0	0
Agrressiveness	0	0	0	0	0	0	Anxiety re head	0	0	0	0	0	0
Ambitiousness	0	0	0	0	0	0	Anxiety re family	0	0	0	0	0	0
Responsibility	1	1	1	1	1	1	Anxiety re occupation	0	0	0	0	0	0
Irresponsibility	1	1	1	1	1	1	Anxiety re other matters	0	0	0	0	0	0
Gaiety	0	3	3	2	2	2	Hysteria (conversion dissociation)	0	0	0	0	0	0
Euphoria	0	3	3	2	2	2	Sex disturbance	0	0	0	0	0	0
Seriousness	2	0	0	0	0	1	Insomnia	0	0	0	0	0	0
Depressive state	0	0	0	0	0	0	Filful sleep	0	0	0	0	0	0
Gregariousness	1	2	2	2	2	2	Increased need of sleep	0	0	0	0	0	0
Seclusiveness	2	1	1	1	1	1	Nightmares	0	0	0	0	0	0
Procentricity	1	1	1	1	1	1	Dreams (accident)	0	0	0	0	0	0
Introspectiveness	1	0	0	0	0	0	Difficulties in concentration and memory	0	0	0	0	0	0
Altrucentricity	1	0	0	0	0	0	Headache	0	0	0	0	0	0
Extrospectiveness	1	1	1	1	1	1	Steady	0	0	0	0	0	0
Sensitivity	0	0	0	0	0	0	Periodic	0	0	0	0	0	0
"Schizoid" traits	1	1	1	1	1	1	Dizziness	0	0	0	0	0	0
Tenseness	0	0	0	0	0	0	Vertigo	0	0	0	0	0	0
Irritability	0	0	0	0	0	0	Palpitation	0	0	0	0	0	0
Vetability	0	2	2	2	2	2	Hyperhidrosis	0	0	0	0	0	0
							Gastrointestinal disturbances	0	0	0	0	0	0
Diagnosis of present injury							Complicating Factors						
Korsakoff syndrome							Compensation						
Contusion of brain, fracture of skull,							Reduction in work ability						
Korsakoff syndrome							Persistence of accidental injury						
Severity of present injury 3							Marital difficulty						
Severity of associated injury 0							Sexual difficulties						
Disproportionate reactions to previous injuries 0							Occupation						
Family history Father alcoholic							Economic difficulties						
Personal psychiatric history Psychopathic personality							War service						
Occupation Laborer							Return to work						

Comment Coma, 20 hours, disorientation, 18 days, amnesia, 18 days Bloody cerebrospinal fluid, severe injury to brain, severe sequelae (?) Categorical person  
 nity classification "Psychopathic" Family insists euphoria represents profound change in personality  
 Admitted 7/13/1942 Discharged 8/29/1942

reaction to previous injuries The reason for inclusion of all these matters in a master work sheet was to keep a multiplicity of possible factors in view in considering each case

This work sheet reflects the data available in the detailed record of each patient The observations which follow are the result of studies of these completed work sheets

## CORRELATIONS, CONCLUSIONS, COMMENT

### SPECIFIC FACTORS

Table 2 presents the distribution of pretraumatic personality ratings (0-1-2-3) with respect to all the traits in the list exclusive of alcoholism

TABLE 2—*Values for Pretraumatic Traits\**

Traits	Distribution of Pretraumatic Ratings			
	0	1	2	3
Asocial attitude	88	13	1	0
Timorousness	44	37	17	2
Prudence	18	24	49	11
Recklessness	51	29	19	3
Aggressiveness	16	42	39	3
Ambitiousness	11	35	45	11
Responsibility	4	18	59	21
Irresponsibility	67	19	15	1
Gaiety	12	34	53	3
Euphoria	82	19	1	0
Seriousness	12	58	29	3
Depressive state	56	15	6	0
Gregariousness	3	25	44	30
Seclusiveness	68	21	11	0
Egocentricity	16	35	40	9
Introspectiveness	65	27	7	3
Altrocentricity	17	41	41	3
Extrospectiveness	9	36	56	1
Sensitivity	42	27	24	9
'Schizoid' tendency	100	2	0	0
Restlessness	42	32	25	3
Tenseness	49	39	22	2
Irritability	60	28	13	1
Excitability	69	27	6	0
Stability	7	26	34	33
Instability	37	37	22	6
Incontinence	101	1	0	0
Impulsiveness	48	34	19	1
Fatigability	74	24	3	1
Apathy	95	6	1	0
Abulia	97	3	2	0
Obsessive compulsive state	76	21	4	1
Hypochondriasis	85	12	3	2
Anxiety, chronic	72	19	9	2
Anxiety attacks	94	5	3	0
Anxiety re head	99	2	1	0
Anxiety re family	80	16	6	0
Anxiety re occupation	97	4	1	0
Anxiety re other matters	94	2	6	0
Hysteria (conversion dissociation)	96	3	2	1
Sex disturbance	82	7	2	1
Insomnia	92	6	3	1
Fitful sleep	94	7	1	0
Increased need of sleep	100	1	1	0
Nightmares	90	10	2	0
Dreams (accident)	101	1	0	0
Difficulties in concentration and memory	100	1	1	0
Headache				
Steady	101	1	0	0
Periodic	93	8	1	0
Dizziness	99	3	0	0
Vertigo	101	1	0	0
Palpitation	100	2	0	0
Hyperhidrosis	98	3	1	0
Gastrointestinal disturbances	100	0	2	0

\* The values in 1 case were inadvertently duplicated, thus accounting for the apparent total of 102 cases this does not materially affect the calculations

and work items. The first column (0) gives the number of patients for whom each trait was given a 0 value. Thus, taking the "asocial" trait as an example, there were 88 patients who were rated as lacking this trait. The next column gives the number of patients (13) in whom the trait was present in a minimal (1) degree, and, the next column, the number of patients in whom this asocial trait was present in a moderate (2) degree. The last column shows that there were no patients in whom this trait was present in a maximal (3) degree. Thus, this table presents at a glance the distribution of values specific for pretraumatic traits.

Table 3 presents the shift in trait values after head injury. This table is multidimensional. It indicates what happened with respect to each trait's pretraumatic rating. It will be noted that there are four comprehensive columns, headed as follows:

Pretraumatic rating	0	Pretraumatic rating	2
Pretraumatic rating	1	Pretraumatic rating	3

Under each of these headings are listed, in three subcolumns, the number of patients who showed a "rise" or a "fall" in value or the "same" value for the trait after trauma. Thus, each master column comprises the data on what happened to the value of that specific personality trait after head injury. To illustrate, one may take the heading "pretraumatic rating 0" and note the trait "timorousness." Reference to table 2 shows that 44 patients were given a pretraumatic rating of 0, 37 were given a rating of 1 (minimal), 17 were given a rating of 2 (moderate), and 2 were given a rating of 3 (maximal). Now, in table 3, under the master heading "pretraumatic rating 0" one can see what happened to the value of the trait "timorousness" for the 44 patients who were rated in table 2 as lacking this trait. It is noted that there was a rise in value for 12 patients. While the degree of rise is not stated, it does appear that 12 patients who lacked timorousness before head injury presented this trait after the injury. It is also noted that there was no change in the pretraumatic value for 32 of the patients. Obviously, there could be no fall in value from an 0 rating. It will be noted under the second master column heading, "pretraumatic rating 1," that of the 37 patients in table 2 who were rated as having a value of 1 (minimal) for timorousness, 13 showed a rise in the value, none showed a fall in value and 24 showed the same value after injury. Under the master heading "pretraumatic rating 2," in table 3, it is noted that of the 17 patients who were graded in table 2 as having a value of 2 (moderate) for pretraumatic timorousness, 1 showed a rise in this value after head injury, 1 showed a fall and 15 had the same value. Under the master heading "pretraumatic rating 3," in table 3, one finds what happened to the value for the trait for the 2 patients noted in table 2 as having

TABLE 3—Changes in Values for Post-Traumatic Traits

Traits	Pretraumatic Rating 0			Pretraumatic Rating 1			Pretraumatic Rating 2			Pretraumatic Rating 3		
	Post Traumatic Value			Post Traumatic Value			Post Traumatic Value			Post Traumatic Value		
	Rise	Fall	Same	Rise	Fall	Same	Rise	Fall	Same	Rise	Fall	Same
Asocial attitude	0	0	88	0	3	10	0	0	1	0	0	0
Timorousness	12	0	32	13	0	24	1	1	15	0	0	2
Prudence	1	0	17	1	0	25	1	2	46	0	0	11
Recklessness	2	0	49	0	8	21	0	4	15	0	0	3
Aggressiveness	0	0	18	0	3	38	0	7	32	0	1	2
Ambitiousness	0	0	11	0	4	32	0	9	36	0	6	5
Responsibility	1	0	3	0	0	18	0	4	53	0	5	16
Irresponsibility	1	0	66	2	1	16	0	0	15	0	1	0
Gaiety	3	0	9	1	2	31	0	15	38	0	2	1
Euphoria	3	0	70	1	8	10	0	1	0	0	0	0
Seriousness	4	0	5	11	1	46	2	2	25	0	0	0
Depressive state	8	0	50	1	0	14	3	0	3	0	0	0
Gregariousness	0	0	1	2	0	21	0	5	39	0	9	21
Seclusiveness	0	0	65	2	0	19	0	2	9	0	0	0
Procentricity	4	0	14	7	0	28	5	0	35	0	1	8
Introspectiveness	11	0	54	3	0	22	0	0	7	0	0	3
Autocentricity	1	0	16	0	8	33	0	9	32	0	0	3
Extropectiveness	0	0	9	1	2	33	0	11	45	0	0	1
Sensitivity	6	0	36	1	1	25	1	1	22	0	0	9
Schizoid tendency	0	0	100	0	0	2	0	0	19	0	0	0
Restlessness	7	0	35	9	1	22	2	4	19	0	1	2
Tenseness	14	0	35	15	2	12	2	5	15	0	1	1
Irritability	16	0	44	11	0	17	3	2	8	0	0	1
Excitability	12	0	37	9	1	17	1	0	5	0	0	0
Stability	0	0	7	2	3	2	0	1	19	0	15	18
Instability	14	0	23	16	1	20	1	2	19	0	2	4
Incontinence	5	0	36	0	1	0	0	0	0	0	0	0
Impulsiveness	3	0	45	2	1	28	1	1	13	0	0	1
Fatigability	31	0	43	1	0	11	0	0	2	0	0	1
Apathy	17	0	78	0	0	6	0	0	1	0	0	0
Abulia	26	0	71	0	0	3	0	0	2	0	0	0
Obsessive compulsive state	10	0	66	2	0	19	1	1	3	0	0	1
Hypochondriasis	11	0	74	3	1	6	2	1	0	0	0	2
Anxiety, chronic	7	0	65	4	1	15	1	2	6	0	0	2
Anxiety attacks	11	0	82	2	0	3	1	0	2	0	0	0
Anxiety re head	31	0	68	1	1	0	1	0	0	0	0	0
Anxiety re family	3	0	77	1	3	12	0	1	3	0	0	0
Anxiety re occupation	1	0	93	2	0	2	1	0	0	0	0	0
Anxiety re other matters	14	0	80	0	0	2	0	0	4	0	0	0
Hysteria (conversion dissociation)	6	0	90	0	1	2	0	0	2	0	0	1
Sexual disturbance	6	0	76	0	1	5	0	1	1	0	0	1
Insomnia	28	0	64	2	1	4	0	1	2	0	0	1
Fitsful sleep	25	0	69	0	1	6	0	0	1	0	0	0
Increased need of sleep	22	0	78	0	1	7	0	0	1	0	0	0
Nightmares	13	0	77	2	1	3	0	1	1	0	0	0
Dreams (accident)	12	0	80	1	0	0	0	0	0	0	0	0
Difficulties in concentration and memory	22	0	78	0	1	0	0	1	0	0	0	0
Headache	16	0	85	0	1	0	0	0	0	0	0	0
Steady	15	0	48	4	1	3	0	0	0	0	0	0
Periodic	36	0	67	0	2	1	0	0	0	0	0	0
Dizziness	16	0	85	0	1	1	0	0	0	0	0	0
Vertigo	6	0	94	0	0	1	0	0	0	0	0	0
Palpitation	2	0	96	2	0	1	0	0	1	0	0	0
Hyperhidrosis	0	0	94	0	0	1	0	0	0	0	0	0
Gastrointestinal disturbance	0	0	94	0	0	1	0	0	1	0	0	0

a value of 3 (maximal) for timorousness. Both appear as having the same value after head injury. Of course, under the master heading "pretraumatic rating 3," no patients will appear in the column headed "rise," because by definition none can have a value greater than 3. However, this column ("rise") was included under "pretraumatic rating 3," as was the column headed "fall" under "pretraumatic rating 0," for purposes of symmetry in making the table.

Examination of table 3 indicates that certain pretraumatic traits tended to change more than others. These traits were timorousness, 27 patients, recklessness, 14 patients, aggressiveness, 12 patients, ambitiousness, 18 patients, gaiety, 23 patients, euphoria, 13 patients, seriousness, 23 patients, depressive state, 12 patients, gregariousness, 18 patients, egocentricity, 18 patients, introspectiveness, 16 patients, and altiocentricity, 18 patients.

Table 3 thus presents a summary of the quantitative changes in specific personality traits after head injury. While all traits showed some change, certain traits showed most prominent changes.

TABLE 4—*Traits in Which Change Occurred After Head Injury in 10 or More Patients*

Trait	Number of Patients		
	Who Showed Post Traumatic Change in Value of Trait	Number of Patients with Rise in Value	Number of Patients with Fall in Value
Timorousness	27	26	1
Recklessness	14	2	12
Aggressiveness	12	0	12
Ambitiousness	18	0	18
Gaiety	23	4	19
Euphoria	13	4	9
Seriousness	23	17	6
Depressive state	12	12	0
Gregariousness	18	2	16
Egocentricity	17	16	1
Introspectiveness	16	14	2
Altrocentricity	18	1	17
Introspectiveness	14	1	13
Sensitivity	10	8	2
Restlessness	24	18	6
Tension	39	31	8
Irritability	32	30	2
Excitability	23	22	1
Emotional stability	15	2	33
Emotional instability	36	31	5
Impulsiveness	15	6	9
Fatigability	44	44	0
Apathy	17	17	0
Abulia	26	26	0
Obsessive compulsive state	13	13	0
Hypochondriasis	20	18	2
Anxiety, chronic	14	12	2
Anxiety attacks	14	14	0
Anxiety re head	34	33	1
Anxiety re other matters	16	14	2
Insomnia	31	30	1
Fitful sleep	26	25	1
Increased need of sleep	22	22	0
Nightmares	21	16	5
Dreams (accident)	13	13	0
Difficulties in concentration and memory	24	22	2
Headache			
Steady	17	16	1
Periodic	51	49	2
Dizziness	28	26	2
Vertigo	17	16	1



Table 4 presents certain data abstracted from table 3. Table 4 lists those traits in which there was a post-traumatic change in 10 or more patients. It indicates the number of patients in whom there was any change and also the number of patients in whom the value for the trait was increased ("rise") or decreased ("fall"). It should be noted in particular by reference to table 3 that a substantial number of patients presented certain traits after trauma which had not been present in the personality before head injury. The data on these traits are summarized in table 5.

TABLE 5—*Traits Appearing After Head Injury for First Time*

Trait	Number of Patients in Whom Trait Appeared Post Traumatically for First Time	Trait	Number of Patients in Whom Trait Appeared Post Traumatically for First Time
Timorousness	12	Anxiety attacks	11
Gaiety	3	Anxiety re head	31
Euphoria	3	Anxiety re other matters	14
Seriousness	4	Hysteria	6
Depressive state	8	Sex disturbance	6
Egoeentricity	4	Insomnia	28
Introspectiveness	11	Filful sleep	25
Sensitivity	6	Increased need of sleep	22
Restlessness	7	Nightmares	13
Tenseness	14	Dreams	12
Irritability	10	Difficulties in concentration and memory	22
Excitability	12	Headache	
Emotional instability	14	Steady	16
Emotional incontinence	5	Periodic	45
Fatigability	31	Dizziness	36
Apathy	17	Vertigo	16
Abulia	26	Palpitation	6
Obsessive compulsive state	10	Gastrointestinal disturbance	6
Hypochondriasis	11		
Anxiety chronic	7		

The changes in personality trait values following head injury are in accord with general clinical experience. The fact that in so many instances the trait was manifest in appreciable degree for the first time (table 5) refutes the oft expressed view that post-traumatic psychiatric symptoms represent a pretraumatic psychiatric liability to such symptoms. This view has been expressed particularly with regard to those patients who presented characteristic psychoneurotic symptoms after head injury.<sup>4</sup> In the present series, it may be noted that a number of patients without evidence of pretraumatic existence of specific psychoneurotic traits manifested such traits post-traumatically. Thus, 10 patients showed obsessive-compulsive symptoms, 11 hypochondriacal symptoms, 6 hysterical symptoms,

4 Lewis, A, in Discussion on Differential Diagnosis and Treatment of Post-convulsional States, Proc Roy Soc Med 35 607-614, 1942

11 clearcut symptoms of anxiety and 31 marked fatigability (neurasthenia), for the first time after injury. It appears, therefore, that the development of psychoneurotic symptoms in patients with head injury does not justify an assumption that such patients had pretraumatic neurotic personalities.

Reference to table 4 shows that the number of patients for whom changes in the trait value followed head injury paralleled the number of those who first manifested the trait after head injury. In table 6 the traits are presented in the order of frequency of involvement (change).

TABLE 6—*Traits in Order of Frequency of Occurrence After Head Injury*

Trait	Total Number	Number of Patients with Post Traumatic Change in Value for Trait	
		Number with Rise in Value	Number with Fall in Value
Periodic headache	51	49	2
Fatigability	44	44	0
Tension	39	31	8
Dizziness	38	36	2
Emotional instability	36	31	5
Emotional stability	35	2	33
Anxiety re head	34	33	1
Irritability	32	30	2
Insomnia	31	30	1
Timorousness	27	26	1
Abulia	26	26	0
Fitful sleep	26	25	1
Restlessness	24	18	6
Difficulties in concentration and memory	24	22	2
Seriousness	23	17	6
Gaity	23	4	19
Excitability	23	22	1
Increased sleep need	22	22	0
Nightmares	21	16	5
Hypochondriasis	20	18	2

The time of appearance of these changes in trait values after head injury varied considerably. In most cases the symptoms (other than headache and dizziness) began to appear shortly after the patient's discharge from the hospital and developed slowly to a maximum in from three to six weeks after discharge. A few patients showed a longer latent period and did not present symptoms until several months after discharge. It may be stated here that these few patients had complicating psychosocial factors in their lives which in their intensity and chronologic appearance tended to parallel the development of symptoms. The appearance of acute neurotic symptoms during hospitalization was infrequent and usually indicated a later intensification and persistence of such symptoms.

The duration of these post-traumatic symptoms also varied. Most had reached their peak at six weeks and were substantially receding at three months. However, approximately 50 per cent of the patients showed some persistence of symptoms at six months, and approxi-

mately 15 per cent of the patients had symptoms which persisted a year or longer. One patient who suffered contusion of the brain and a brief period of unconsciousness, with a gross residual cosmetic defect of his forehead, showed irritability two years after head injury.

The duration of incapacity for work paralleled the persistence of symptoms, although most patients returned to work before they were entirely free of symptoms.

#### PERSONALITY CATEGORIES

In order to test popular conceptions concerning the relationship between categorical personality classifications, such as pretraumatic, normal, psychoneurotic, psychovariant and psychopathic personalities, as well as to test my previous conclusions about such categories, each patient in this study was classified under one of the following four headings, each of which has been previously defined as follows<sup>1</sup>

*Normal Personality*—A person who is in harmony with himself and his environment, is virtually free of psychoneurotic traits and other personality imbalances, is not habitually in conflict with the ethical and social standards of society, is free of addiction to alcohol, maintains satisfactory personal, social and occupational adjustments and presents a general integration of objectives and behavior. This does not exclude the possible existence of some personality bias, such as egocentricity or timidity, or even a history of brief transient neurotic symptoms.

*Psychopathic Personality*—A person who has shown extreme failure in social and intrapersonal adaptation, associated with impulsiveness, defective self control, lack of fixity of purpose, instability of effort and undependability in his work. In this category are wide variations. There may or may not be associated psychoneurotic phenomena. It is possible to make an unlimited series of subtypes of the psychopathic personality. I have selected seven inferior, alcoholic, affective, aggressive, criminal, schizoid and miscellaneous types. As these subtypes are not discussed in the present study, they are not defined here.

*Neurotic Personality*—A person whose behavior and experience are substantially affected by the existence of traits or symptoms which characterize the generally accepted psychoneurotic syndromes of neurasthenia, hypochondriasis, anxiety neurosis, obsessional neurosis and hysteria.

*Personality Variant*—A person who, while not psychotic, frankly psychoneurotic or psychopathic, has appreciably more weighting of the personality than the average normal subject. Such patients represent deviations from the average. The personality bias includes such traits as timidity, egocentricity, irritability, cantankerousness, hypersensitivity, moodiness, emotional lability, solemnity or general light heartedness.

The distribution of categorical personality diagnoses was as follows. Fifty-one patients were classified as normal, 13 as psychoneurotic, 14 as psychopathic and 23 as psychovariant personalities.

Table 7 presents the values for a list of traits on which the diagnoses of "psychopathic personality" were based. It may be noted that alcoholism was present in 11 of these patients, although in 1 it was relatively

mild Patient B had many psychoneurotic symptoms, as well as addiction to alcohol, but his gross character defects led to his classification as a "psychopathic personality." Only 2 patients were delinquent. One of these was a young man who could not refrain from following his impulses to drive other persons' automobiles. In 3 of the patients (S, J and C) alcoholism of varying degree was coupled with sensitiveness, restlessness and tenseness. Seven of these patients had a poor work record, 5 had associated alcoholism. Eight exhibited recklessness, 5, aggressiveness, 10, irresponsibility, 7, egocentricity, and 7 impulsiveness.

The "psychoneurotic" patients all had good work records and were free of alcoholism. Whereas the average value for "sensitiveness" in

TABLE 7—*Special Trait Values for Pretraumatic Psychopathic Personalities\**

Patient	Alcoholism	Unsteady Work Habits	Asocial Traits	Recklessness	Aggressiveness	Irresponsibility	Ego centrality	Emotional Instability	Impulsiveness
V	0	2	2	2	2	2	2	3	2
Mc	3	2	1	2	0	2	0	0	2
P	0	2	0	2	3	2	3	2	3
K	2	0	0	2	1	2	0	0	2
G	2	1	0	2	1	2	2	1	1
C	2	1	0	1	0	1	1	1	1
F	2	0	0	2	2	2	2	2	2
W	3	2	0	1	1	2	1	1	2
T	3	2	0	0	2	0	1	1	0
K	3	3	0	0	0	2	1	1	1
S	3	0	0	2	1	1	1	1	0
J	2	1	0	0	0	1	3	0	0
C	1	1	0	2	2	2	2	3	2
B	3	2	0	1	1	3	2	2	0

\* Rated on a scale of 0 to 3

"psychopathic personalities" was less than 1 (on the scale of 0 to 3), the average value for this trait in the "psychoneurotic subjects" was in excess of 2.

The "normal" subjects also had good work records and were essentially free of alcoholism. None had a value greater than 1 for any of the recognized psychoneurotic traits (fatigability, hypochondriasis, anxiety states, obsessive-compulsive states and hysteria). In general they were emotionally stable. There were no evidences of restlessness, tenseness, irritability or excitability. The traits of prudence and timorousness were much higher in these patients than in the psychopathic personalities in whom they were virtually absent. The greatest differences between individuals in this group of normal personalities was in regard to the traits of gregariousness, ambitiousness, extropection, gaiety and seriousness.

Chart 1 presents the comparative average values (on a scale of 0 to 3) for each of the 60 personality items for the four pretraumatic

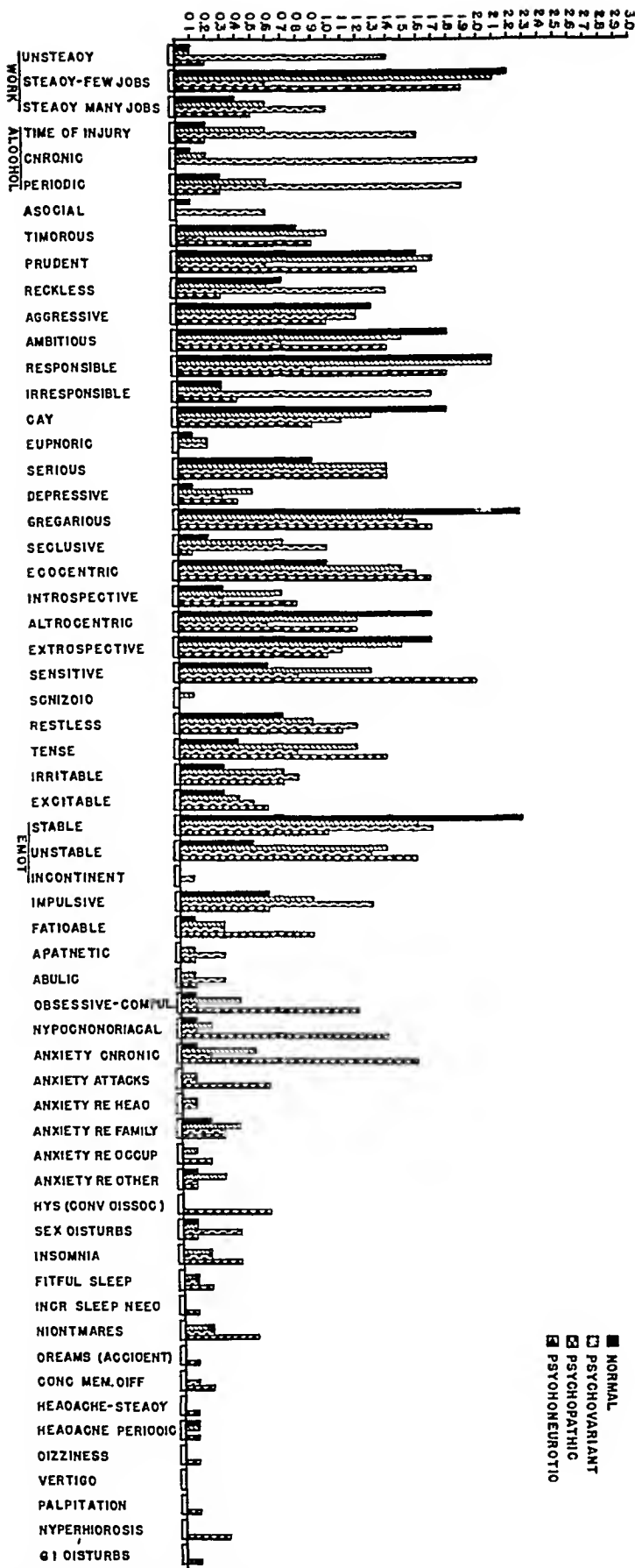


Chart 1—Comparison of average values for each of 60 personality characteristics of patients with pretraumatic psychoneurotic, psychopathic psychovariant and normal personalities

categories (normal, psychovariant, psychopathic, psychoneurotic) The key is given on the chart The data are thus presented on which the categorical distinctions are based

Chart 2 presents a comparison of the pretraumatic and post-traumatic average values for each of the 60 personality characteristics of those patients who were classified as having a pretraumatic normal personality Charts 3, 4, and 5 present similar data on the patients with pretraumatic psychoneurotic, psychovariant and psychopathic personalities

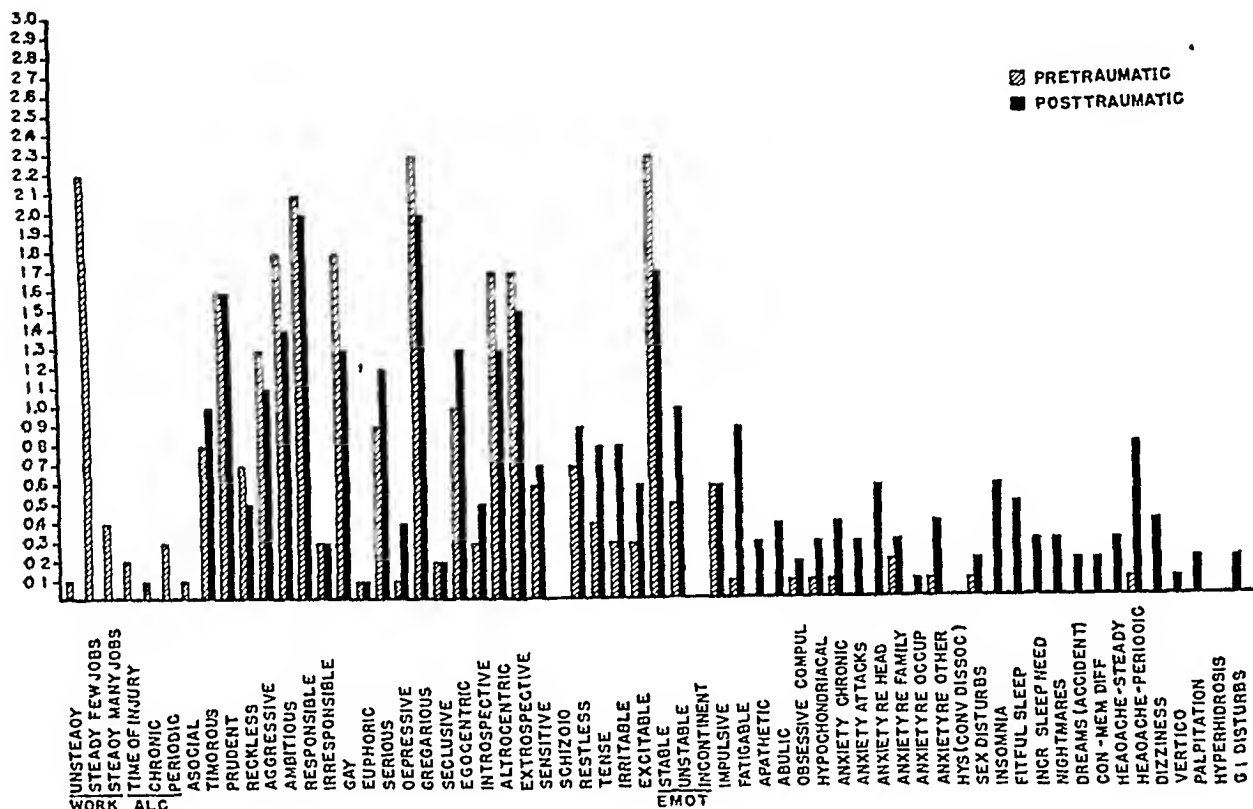


Chart 2—Comparison of the pretraumatic and post-traumatic average values for each of 60 personality characteristics of patients with pretraumatic normal personality

In this chart, and in charts 3, 4 and 5, pretraumatic values are represented by hatched rectangles, post-traumatic values, by solid rectangles

Chart 6 is derived from charts 2 to 5 It presents those traits in which there was a change of 10 per cent or more between the pretraumatic and the post-traumatic average value for any 4 personality categories It will be noted that the pretraumatic normal personalities showed such a change in respect to 26 items The average for the change of values for pretraumatic normal personalities was approximately 14 per cent The psychovariant personalities showed a change in respect to 19 items and an average change of 13 per cent The psychopathic personalities showed a change in respect to 6 items, with an average change of 12.5 per cent The

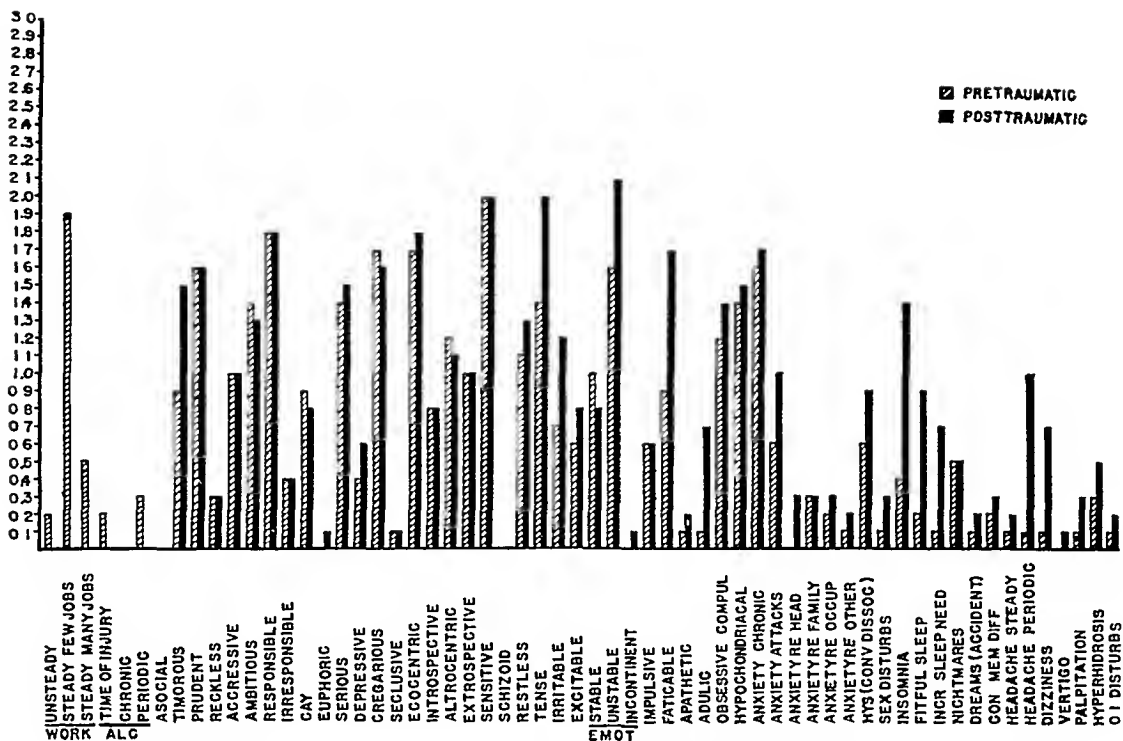


Chart 3—Comparison of the pretraumatic and post-traumatic average values for each of 60 personality characteristics of patients with pretraumatic psychoneurotic personality

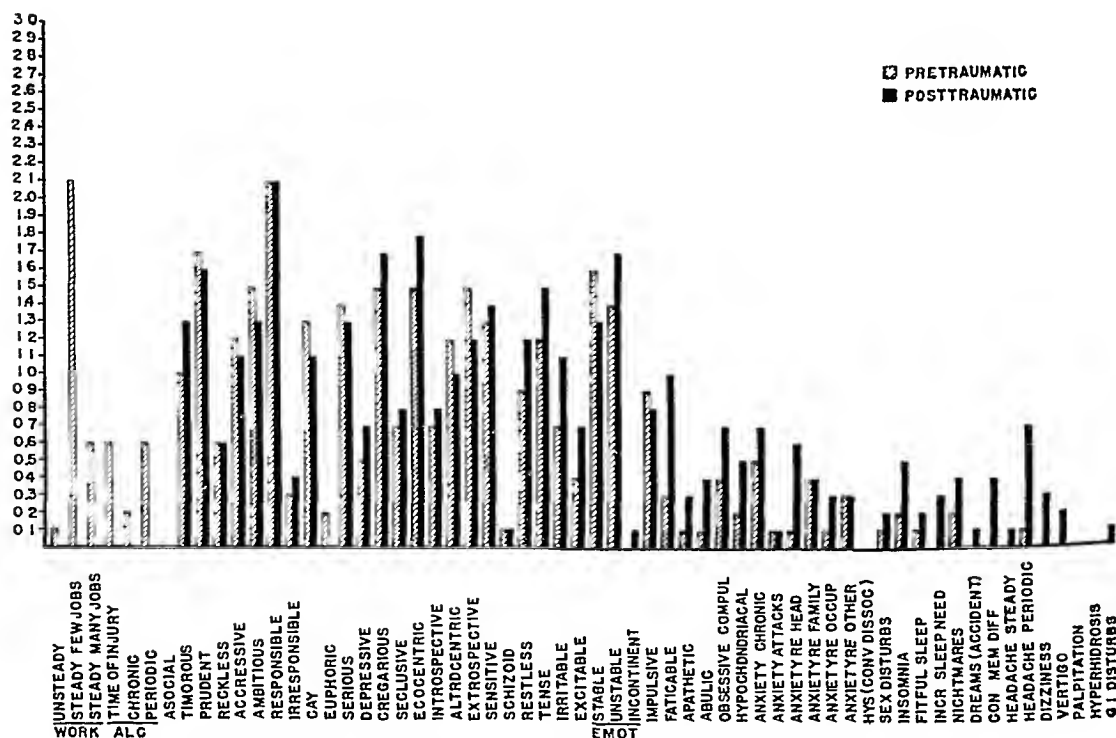


Chart 4—Comparison of the pretraumatic and post-traumatic average values for each of 60 personality characteristics of patients with pretraumatic psychovariant personality

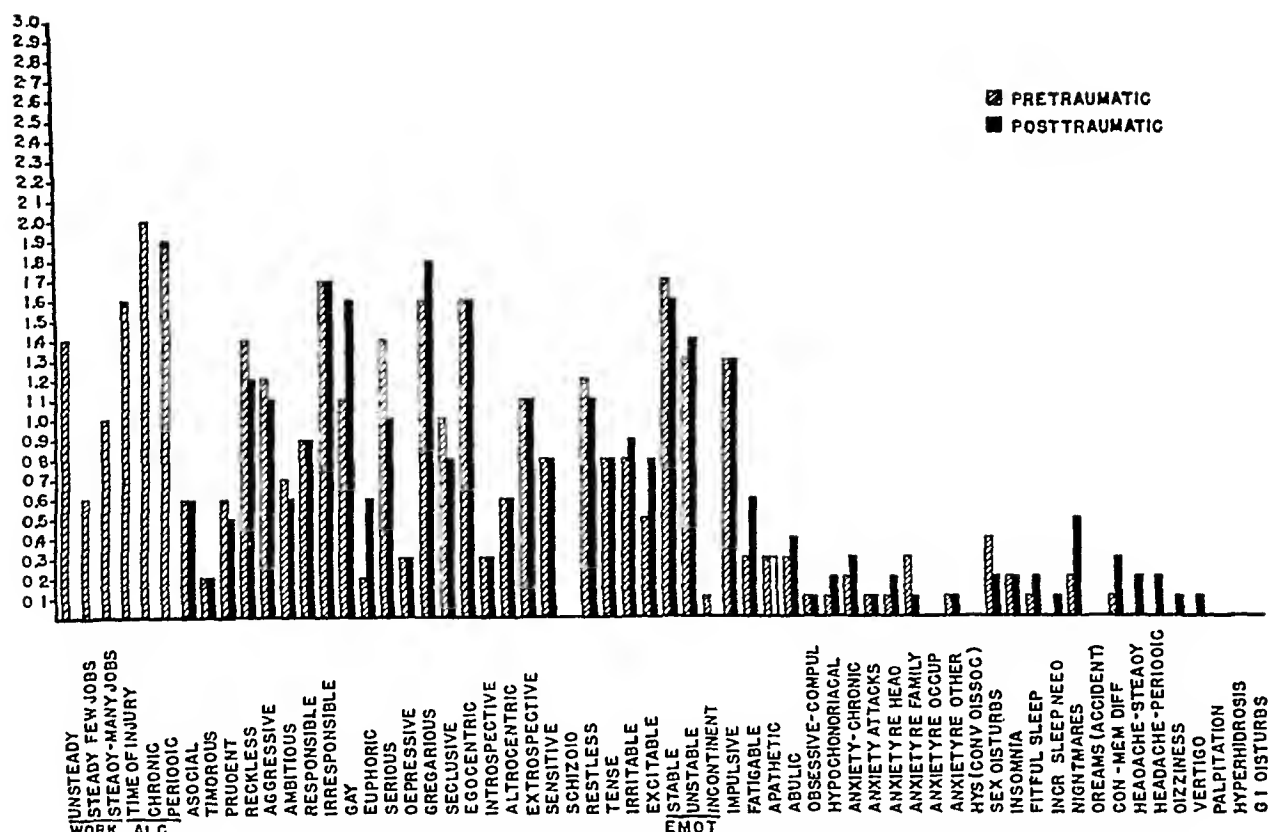


Chart 5—Comparison of the pretraumatic and post-traumatic average values for each of 60 personality characteristics of patients with pretraumatic psychopathic personality

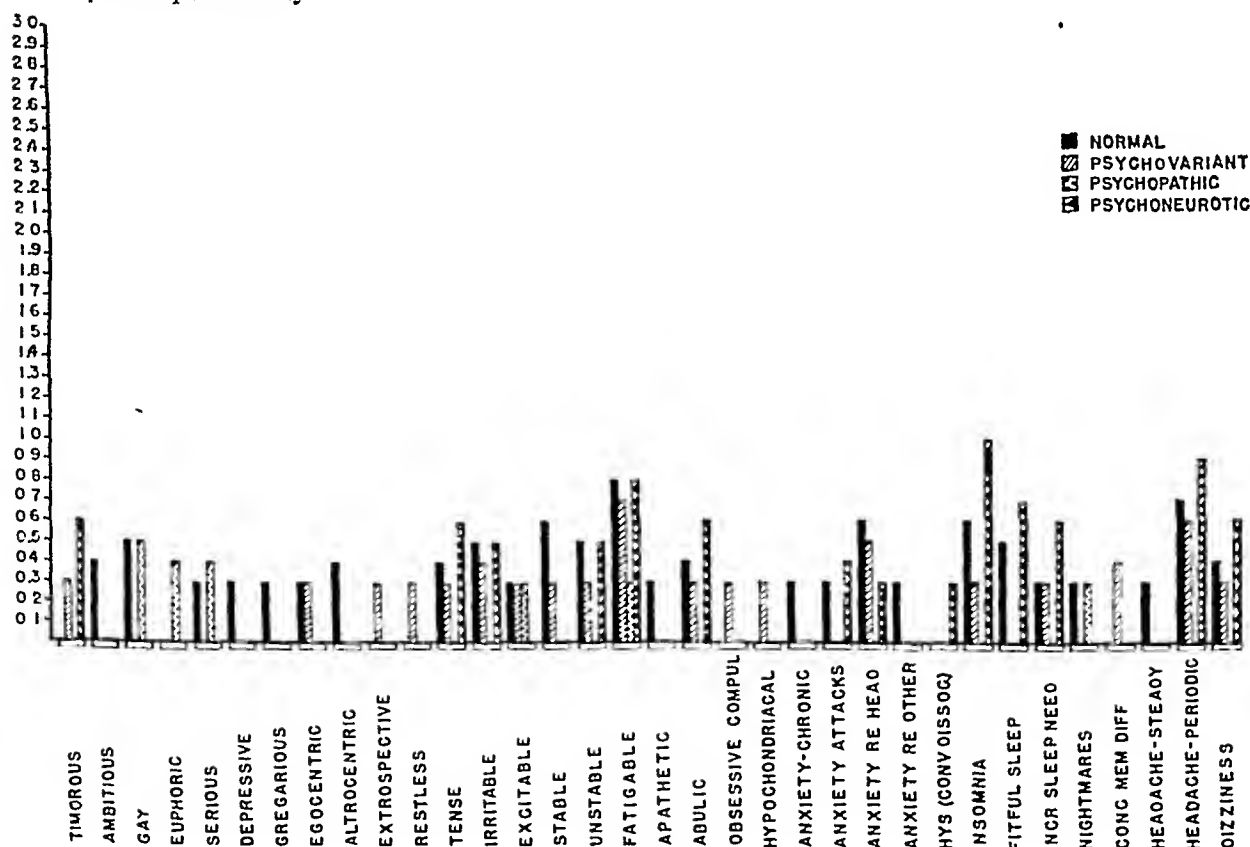


Chart 6—Comparison of those traits in which significant differences (10 percent or more) were found between the pretraumatic and the post-traumatic average values for patients with pretraumatic psychoneurotic, psychopathic psychovariant and normal personalities



psychoneurotic personalities showed a change in respect to 14 items, with an average change of 20 per cent. It should be kept in mind that these psychoneurotic personalities had such high pretraumatic values for the special traits which led to the categorical diagnosis that there was little, or no, room left for change in value. The average change of value for the combined psychoneurotic, psychovariant and psychopathic personality groups was 13 per cent. When this is compared with the average change of value of 20 per cent for the psychoneurotic personalities, it appears that there was approximately a 50 per cent greater change for the psychoneurotic personalities than the average change for the other three categories.

In the psychoneurotic group the greatest changes took place with respect to fatigability, disturbances in sleep, headache and dizziness. It would appear, then, that pretraumatic psychoneurotic personalities may have a greater liability to the development of such post-traumatic symptoms. However, it will be noted that the "normal personalities" run a close second with respect to most of the changes and equal the psychoneurotic personalities with regard to changes in values for fatigue and exceed them with respect to other items.

When attention is directed to the generally recognized neurotic traits, the following correlations appear. The only trait which was substantially affected in all four personality groups was that of fatigability. The average change of values (on a scale of 0 to 3) in each of these groups was as follows:

Normal	0.8	Psychovariant	0.7
Psychoneurotic	0.8	Psychopathic	0.3

Only the psychovariant personality group showed appreciable changes (0.3) with respect to obsessive-compulsive and hypochondriacal symptoms.

The changes in respect to the categories of anxiety are presented in table 8.

It appears, then, that psychoneurotic personalities were slightly more liable to development of anxiety attacks than were other personality types, although the figure for the normal personalities suggests an even greater propensity in such persons because that group was entirely free of anxiety attacks before head injury. It is to be noted, also, that anxiety concerning the head was greater among the normal and psychovariant personalities than among the psychoneurotic personalities.

The psychopathic personalities showed the greatest changes in respect to an increase in or development of gaiety and/or euphoria and a decrease in seriousness. This cannot be considered a basis for generalization, as the particular patients who showed these changes not

only had suffered surgically severe head injury (fractured skull, contused or lacerated brain, intracranial hematoma) but also had histories of substantial chronic alcoholism. It is my impression that the preceding chronic alcoholism played a large part in contributing to the reactions of gaiety and euphoria, for such were not seen to an appreciable degree in patients in other personality categories who had suffered equally severe surgical head injury. It should be added that it was the same few psychopathic personalities with post-traumatic euphoria who were suspected of having post-traumatic dementia. Denny-Brown<sup>2</sup> noted that the elimination of patients over 55 years of age who had chronic alcoholism eliminated cases of post-traumatic dementia. He noted, further, by reference to the case of a normal, intelligent youth who had suffered gross laceration of both frontal lobes with a buzz saw, that the absence of a post-traumatic dementia in that case threw "doubt on the ability of trauma alone to induce persistent dementia in a healthy brain." By the same token, it is

TABLE 8—*Correlations of Personality Categories with Average Change in Values for Types of Anxiety*

Type of Anxiety *	Personality Category			
	Normal	Psycho-neurotic	Psycho-variant	Psycho-pathic
Chronic	0.3	0	0	0
Attacks	0.3	0.4	0	0
Re head	0.5	0.3	0.4	0
Re other matters	0.3	0	0	0

\* The trait values are rated on scale of 0 to 3

probable that severe injury to a healthy brain will not in itself result in post-traumatic euphoria. However, this entire field is subject to contributions which may be offered by the recent work in surgical lobotomy. The euphoria which appeared in the patients with psychopathic personalities in this series who had received gross injuries may, on the other hand, have been expressive of an underlying irresponsibility and obliviousness to the patient's own welfare, factors which are apparent in most psychopathic personalities.

It appears, then, that patients with the pretraumatic psychoneurotic personality may not exhibit a striking aggravation of neurotic symptoms after head injury but will in general show a greater post-traumatic reaction than those in the other groups. This conclusion is supported by the data in table 9, which presents correlations between pretraumatic personality characteristics and clinical approximations of the severity of the psychiatric sequelae of the head injury (on a scale of 0 to 3). It appears that the occurrence of sequelae is most probable in psychoneurotic personalities, next most probable in psycho-

variant personalities, less probable in normal persons and least probable in psychopathic personalities

#### SEVERITY OF HEAD INJURY

It has been pointed out by Denny-Brown<sup>2</sup> that the assessment of the severity of a head injury requires inclusion not only of the immediate post-traumatic surgical, as well as the behavioral, state but also various complicating psychologic factors. Of the patients in the present study, 21 exhibited prolonged disorientation, ranging from five hours to over a week. Of this group there were 3 patients who had bloody cerebrospinal fluid, fractured skull or intracranial hematoma and who had been subjected to craniotomy and associated neurosurgical treatment. Two of these patients presented maximal post-traumatic mental

TABLE 9—*Estimated Severity of Sequelae of Head Injury Correlated with Pre-traumatic Personality Type*

Personality Type *	Severity of Sequelae to Head Injury									Total No of Pa tients with Sequelae of Any Degree	Per Cent of Orig inal Group with Se quelae
	Total No of Pa tients	0		1		2		3			
		No of Pa tients	Per Cent of Total	No of Pa tients	Per Cent of Total	No of Pa tients	Per Cent of Total	No of Pa tients	Per Cent of Total		
Normal	51	26	51	9	18	9	18	7	14	24	48
Psychopathic	14	8	57	2	14	1	7	3	21	6	42
Psychovariant	23	9	39	6	26	4	17	4	17	14	60
Psychoneurotic	13	5	39	2	15	1	8	5	39	8	39

\* Rated on scale of 0 to 3

symptoms. Both had been rated as pretraumatic psychopathic personalities. One of these patients underwent a gross personality change. Previous to his head injury he had been seclusive and secretive, was substantially alcoholic but had a fair work record and was moderately responsible in his obligations to his work and family. After his head injury he became expansive, circumstantial, euphoric and emotionally unstable. He confided freely in his family and had no insight concerning his changed personality. He had difficulty with his concentration and memory. This was at its worst in the first two months after head injury, and, although there was gradual improvement, there was some persistent intellectual defect, even at nine months. It is of interest to note that he had no post-traumatic neurotic symptoms of any sort and no dizziness or headache. This man was 43 years of age. He worked as a laborer. His non-neurotic change in personality suggests, as previously noted, an organic cause, probably the result of trauma superimposed on a brain which had already been made vulnerable by chronic alcoholism. Although there was some litigation pending in this case, it did not seem to have any influence

on the symptoms. The patient was too oblivious to most things to be particularly concerned with such an issue.

The second of this group of severely injured patients, aged 32, was an irresponsible male laborer with a history of pretraumatic alcoholism, gross irresponsibility, emotional instability and multiple neurotic symptoms. After his head injury he manifested an increase in fatigability, a decided exacerbation in the frequency and severity of anxiety attacks (present minimally before injury), increased hypochondriasis, preoccupation concerning the state of his heart and lungs, intense anxiety concerning his head, nightmares, difficulties in concentration and memory, headaches, both steady and periodic, dizziness, and vertigo. On the other hand, he showed an increase in emotional stability (except for his acute neurotic symptoms) and became less irritable and somewhat more responsible. He exhibited an increase in gaiety, which may be compared with the euphoria of the previous patient. Prior to his injury he was having difficulties in his marriage and work. His electroencephalogram remained abnormal for several months but cleared completely in four months. In such a case it is impossible to select one factor as the sole cause of the sequelae. The development of a state of gaiety disproportionate to the situation suggests persistent damage to the brain. Or, again, it may be a summation of the effect of severe trauma on the brain of a chronic alcohol addict. It is of interest to note the parallel development of both neurotic symptoms and increased emotional stability.

The third patient was a 20 year old man. In addition to a compound fracture of the skull and an extradural hematoma, he had sustained a fracture of his left clavicle and humerus, with palsy of the radial nerve and ankylosis. He had been categorically rated as a pretraumatic "normal" personality. He had a good work history and was guileless, responsible, serious, gregarious, altrocentric, rather sensitive and irritable and free of neurotic traits. He presented no psychiatric sequelae to the head injury, not even a headache. Previous to his head injury he had been subject to occasional dizziness, but he suffered no increase in this disturbance. He returned to work five months after his head injury, although his arm was not yet healed. Why did he not exhibit psychiatric sequelae? The answer is not clear. As there was no persistent intellectual impairment after head injury and no euphoria or gaiety, I am not inclined to postulate persistent damage to the brain, which might have made him oblivious to his state. The brain of a nonalcoholic youth of 20 is probably less vulnerable than that of a chronic alcohol addict of an older age group. The severe injury to the arm would have justified a substantial state of anxiety, yet he showed virtually none—not even concerning the arm itself. In a search for a possible explanation inquiry was

made concerning constitutional factors. He had long been at odds with his family because of their general irresponsibility and obliviousness to the responsibilities of everyday life. Both parents were happy-go-lucky and improvident. Could an injury to the brain have mobilized such latent tendencies in him? Certainly, there is no evidence to support such a speculation, nor can one invoke the categorical pretraumatic diagnosis of "normal," because a scrutiny of the details of his personality shows that in the "normal" group he was one of the most serious and might thus have been expected to react with greater gravity to a difficulty. This case illustrates the difficulty, or impossibility, of relating psychiatric sequelae to the surgical severity of an injury to the brain.

In addition to these 3 patients, there were 9 who were considered to have suffered very severe acute injury to the brain, as judged by prolonged coma, disorientation and amnesia, with grossly bloody cerebrospinal fluid in each case, coupled with fracture of the skull in 6. Three patients had been subjected to craniotomy for debridement of compound, comminuted fractures. The average severity of psychologic sequelae (including headache, dizziness and work disability), on a scale of 0 to 3, was 1.3. The categorical pretraumatic diagnoses of these 9 patients were as follows: psychopathic personality, 1 patient; psychovariant personality, 3 patients; normal personality, 5 patients; and neurotic personality, none.

Nineteen patients were classified as having suffered moderately acute injury to the brain. They had all manifested substantial disturbances of consciousness, orientation and memory, in addition, 14 had grossly bloody cerebrospinal fluid. Eleven had skull fractures. The average severity of psychologic sequelae in this group was 1.3, a figure identical with that for the more severely injured group.

Minimal acute injury to the brain was sustained by 70 patients. The average severity of sequelae in this group was 0.8. This figure is definitely less than that for the preceding group. It may be argued, therefore, that there is some increased statistical probability of psychologic sequelae of patients with the grosser acute head injuries. This does not prove that the psychiatric symptoms are the direct result of injury to the brain as such. When there has been compound fracture of the skull or other gross surgical injuries, the necessarily prolonged stay in the hospital might well have an impressive psychologic effect on the patient.

Table 10 tests the possibilities by a correlation of the severity of injury to the brain and the severity of sequelae. From the table it is apparent that there is not a rigid relationship between the severity of the cerebral injury and the severity of sequelae except for the

psychopathic personalities In this group it will be noted that each of the 3 patients with severe sequelae had suffered severe injury to the brain Euphoria developed in 2, with evidences or suggestions of dementia The changes in these patients have already been described, as was the state of the patient with severe damage to the brain, who had only minimal sequelae In the group with "normal" pretraumatic personalities, there were 7 patients with severe injury to the brain, of these, 3 had no sequelae, 1 minimal sequelae, 1 moderate sequelae and 2 maximal sequelae In the same group it should be noted that 4 of the 7 patients who exhibited maximal sequelae had sustained only

TABLE 10—*Estimated Severity of Injury to Brain Correlated with Estimated Severity of Sequelae in Various Personality Categories*

Personality Type	Severity of Sequelae *	Severity of Brain Injury †		
		1	2	3
		Number of Patients		
Normal	0	20	4	3
	1	4	4	1
	2	6	2	1
	3	4	1	2
Psychoneurotic	0	5	0	0
	1	2	0	0
	2	0	1	0
	3	5	1	0
Psychopathic	0	7	1	0
	1	1	0	1
	2	1	0	0
	3	0	0	3
Psychovariant	0	6	1	2
	1	3	3	0
	2	3	0	1
	3	1	3	0

\* Rated on scale of 0 to 3

† Rated on scale of 1 to 3

minimal injury to the brain None of the patients with pretraumatic psychoneurotic personalities sustained severe injuries to the brain, and only 2 sustained moderate cerebral injuries Yet it should be noted that the psychoneurotic patients did show a larger portion of sequelae than either of the other groups In the group of 3 patients with psychovariant personalities who sustained severe injuries to the brain, only 1 had even moderate sequelae, while 2 had no sequelae It appears, thus, from table 10 that, except for the psychopathic personalities, there is little correlation between the severity of the injury to the brain and the sequelae of such injury

#### COMPLICATING FACTORS

When a person sustains a head injury, he may in addition, and often does, suffer injury to other parts of his body The persistence of such associated injury contributes to a continuance of the patient's interest in himself This may be particularly so if such associated

injury prevents a return to work. On the other hand, the persistence of an associated injury or injuries appears in some cases to act as a distraction. In every case of head injury, then, one must take into account the possible effect of an associated injury, if such occurred. In general there was a high correlation of persistence of associated bodily injuries, prolonged work disability and persistence of psychiatric symptoms.

One must not lose sight of the fact that a head injury always involves a person as such rather than an arbitrarily defined part of that person. Such a person can be understood only in the light of his constitution and conditioning experiences. His reaction to a head injury, as to any incident in his life, is affected by what he was previous to that incident. In the present studies notice was taken of the possible existence of the following complicating psychosocial factors:

Marital or domestic difficulties

Sexual maladjustments

Occupational stresses and hazards

Financial difficulties

Impending induction into the armed forces

Under existing social legislation, provision is usually made for compensation to those injured in the course of their occupations. In addition, the law requiring that motor vehicles carry insurance to provide compensation in cases of bodily injury makes the frequency of litigation high. It was noted, therefore, with respect to each case whether there was any issue of compensation or litigation.

Table 11 presents an analysis of the data on all patients in this study who had sequelae of the head injury. In this table, the personality type, the severity of the sequelae and the severity of the injury to the brain are presented, together with data concerning any associated injury, the existence of compensation or litigation problems, other complicating factors and the time of return to work.

From a study of this table, it is obvious that there was a high correlation between the existence of pending litigation, continuing work disability and persistent psychiatric symptoms (sequelae). In general, this is greatly out of proportion to the estimated severity of the cerebral injury as such. The interpretation of this phenomenon is open. It would appear that the existence of litigation at the very least tends to maintain the patient's focus on the subject, particularly as legal processes are extended. However, contrary to some judgment, the termination of litigation does not generally terminate the symptoms promptly. It undoubtedly does have a salutary effect on the symptoms to the degree that one factor which has tended to keep the patient's mind on himself has been eradicated. In no case in this series was

TABLE 11—*Analysis of Data on Patients with Sequelae to Head Injuries*

Personality	Severity (Scale 0-3)		Associated Injury	Compensation Litigation	Other Complicating Factors	Return to Work
	Sequelae	Brain Injury				
Psychopathic	1	1	—			Prompt
	1	3	—		Dementia (?)	2 mo
	2	1	—	+	Marital trouble	1 mo
	3	3	—	—		1 yr ++
	3	3	—	+		1 yr +
	3	3	—	+	Abnormal electrocardiograph—4 mo	9 mo
Psychovariant	1	1	—	—		1 mo
	1	1	—	—	Marital trouble	1 wk
	1	1	—	—	Persistent headache	3 mo
	1	2	Compound fracture of both legs	—	Dizziness—12 mo	1 yr
	1	2	—	—		2 mo
	1	2	Torn tibial tubercle	+		Over 6 mo
	2	1	—	+	Financial difficulties	Over 6 mo
	1	2	—	—	Domestic difficulties	Over 6 mo
	2	1	—	—		1 mo
	2	3	Paralysis of 6th and 7th nerves	—		Over 6 mo
	3	1	Synovitis (knee)	+	Marital trouble	3 mo
	3	2	Ulcers and abrasion of leg	+	Occupational hazards—fire captain	6 mo
	3	2	Amputation—toes and foot	+	Occupational hazards	Over 7 mo
	3	2	—	+	Sexual and financial difficulties	4 mo
Psychoneurotic	3	2	Fracture of zygoma	+	—	3 mo
	3	1	Burns	+	Occupational hazards—fireman	6 mo +
	3	1	Laceration of face, deafness (8th nerve)	+	—	3 mo
	3	1	Marked dizziness	+	—	1 mo
	3	1	—	+	Marital trouble	3 wk
	2	2	Sprain of back	+	—	2 mo
	1	1	—	—	Financial	3 mo
	1	1	Fractured nose	—	—	1 mo
Normal	3	3	Depression of skull above eye	+	Cosmetic defect	2 mo
	3	3	Squint, sprained wrist	+	Persistent squint, etc	1 yr
	3	1	Multiple lacerations	+	Occupational hazards—fireman	9 mo
	3	1	—	+	Illegitimate pregnancy, etc	3 mo
	3	1	Tinnitus	+	—	7 mo +
	3	1	—	+	Fireman—recovery on change of jobs	3 mo
	3	2	Fractured ribs, 7th nerve	+	—	6 mo +
	2	3	—	—	Impending induction	3 mo
	2	1	Lacerated scalp	+	Marital trouble	2 mo
	2	1	Infection of leg with sinus tracts	+	Marital and financial trouble	2 mo
	2	1	—	+	Sexual difficulty	3 mo
	2	1	Back sprain	+	—	3 mo
	2	1	—	+	Occupational hazards—fireman	4 mo
	2	1	Back sprain, sear over eye	+	—	3 mo
	2	2	Abrasions	+	—	3 mo
	2	2	—	+	—	2 wk
	1	1	—	—	Impending induction	3 mo
	1	1	—	+	Occupational—police-man	4 mo
	1		—	—	—	1 mo
	1		—	—	—	1 mo
	1	1	—	—	—	1 mo
	1	1	—	—	3 sons in military service	1 mo
	1	2	—	+	—	1 mo
	1	2	Fractured ribs	—	Diabetes, thyroid, etc	4 mo
	1	2	Paralysis, 5th and 6th nerves	—	Marital trouble	3 mo
	1	2	—	+	—	1 mo
	1	3	Epilepsy and cosmetic defect	—	—	1 mo



a diagnosis of malingering made or suspected. It should be added, as has been stated before, that most patients returned to work long before litigation was terminated.

When compensation was being paid to an injured person on the basis of industrial accident insurance, the convalescence was usually much longer. This was particularly noticeable in cases of persons with hazardous occupations, such as firemen and police officers.

In order to test the distributional relationships involving litigation to see whether there was any particular incidence or weighting, a scattergram (table 12) was devised in which various combinations

TABLE 12—*Scattergram, Showing Number of Patients with Various Combinations of Factors\**

	N	O	P	Q		N	O	P	Q
ACGIK	0	1	1	1	BCGIK				1
ACGIL					BCGIL				
ACGIM					BCGIM			1	
ACGJK	1				BCGJK	1	1		
ACGJL			1		BCGJL				
ACGJM			1		BCGJM				
ACHIK		1			BCHIK	2	1		
ACHIL					BCHIL		1	1	
ACHIM		1			BCHIM				1
AOHJK	5				BOHJK	7		1	
ACHJL	1		3	1	BCHJL	1	1	1	
ACHJM					BCHJM			1	
ADGIK					BDGIK	2			
ADGIL					BDGIL				1
ADGIM			1		BDGIM			1	1
ADGJK					BDGJK	2	1	1	1
ADGJL					BDGJL	1	1		
ADGJM					BDGJM				1
ADHIK	1	2		1	BDHIK	1	1		2
ADHIL		1		2	BDHIL		3	1	1
ADHIM					BDHIM			2	
ADHJK	4				BDHJK	12	2	4	1
ADHJL		1			BDHJL		4		
ADHJM					BDHJM		1		

\* A, indicates litigation, B, no litigation, C, problems, D, no problems, G, chronic alcoholism, H, no alcoholism, I, associated trauma, J, concussion only, K, coma of less than thirty minutes' duration, L, coma of less than ninety minutes' duration, M, coma of more than ninety minutes' duration, N, disorientation of less than one hour, O, disorientation of less than three hours, P, disorientation of less than twenty four hours, and Q, disorientation of more than twenty four hours.

were correlated against four degrees of disorientation. In all, 31 patients were engaged in litigation and 70 patients were not. In the left half of the scattergram litigation is the one common factor for the 31 patients dealt with there, in the right half of the scattergram the absence of litigation is the one common factor. The other factors considered are existence of other complicating psychosocial factors, nonexistence of psychosocial factors, existence of chronic alcoholism, absence of alcoholism, associated bodily injury, clinical diagnosis of simple concussion, and coma of less than thirty minutes' duration, ninety minutes' duration or more than ninety minutes' duration.

These items were given key letters, as follows: A, existence of litigation, B, absence of litigation, C, existence of complicating psycho-

social factors other than litigation, D, absence of complicating psychosocial factors other than litigation, G, chronic alcoholism (pre-traumatic), H, absence of alcoholism, I, associated bodily injury, J, clinical diagnosis of concussion, K, coma of less than thirty minutes' duration, L, coma of less than ninety minutes' duration, M, coma of more than ninety minutes' duration

Every possible combination of these items was arranged, and the number of patients with each combination was noted. These were then correlated with the duration of disorientation following the head injury. There were four categories of disorientation, arranged according to the following key letters: N, disorientation of less than one hour, O, disorientation of less than three hours but more than one hour, P, disorientation of less than twenty-four hours but more than three hours, Q, disorientation of more than twenty-four hours.

From this scattergram it appears that none of these factors other than *A* or *B* were present by chance in such large degree as materially to weight the data.

*Comment*—It is apparent from the foregoing data that the psychiatric sequelae of head injury cannot be related to one particular factor. It is obvious that neither severe acute injury to the brain nor a heavily burdened personality will in itself explain the appearance and persistence of psychiatric sequelae as such. Certainly, some of the patients in this series who were heavily burdened with neurotic traits recovered from the acute head injury without sequelae. I was particularly interested not only in ascertaining if possible why patients have sequelae but also why some patients did not have sequelae. The reasons that patients did not exhibit sequelae were about as complex as the reasons that some did. On the whole, however, the patient who was altrocentric rather than egocentric, social minded and endowed with a high sense of responsibility was most likely to escape substantial sequelae despite the fact that such a person might be heavily burdened with neurotic traits.

In part I<sup>1</sup> it was noted that among the patients presenting post-traumatic mental symptoms there was a slight predominance of pretraumatic neurotic personalities. It was argued, however, that the statistical difference between such a group and other personality categories was insignificant. Those statements must be modified in the light of the observations which appear in the present paper, and which have been based on more intensive personality study. The group of pretraumatic psychoneurotic personalities as a whole did show a substantially greater degree of psychiatric sequelae than did other groups. However, it must be stressed that this difference is not great enough to permit any generalizations other than those applying to large series.

of cases. Pretraumatic normal personalities closely approached the psychoneurotic personalities in the degree of psychiatric sequelae.

The syndromes following trauma to the head cannot be categorically related to the acute head injury as such, to the pretraumatic personality or to complicating factors. There appears to be little validity for continuing the commonly accepted term "postconcussion syndrome," because if such a term had validity there should be a relationship between severity of the concussion as measured by the duration of unconsciousness and the severity of the sequelae. No such relationship has been demonstrated. Denny-Brown<sup>2</sup> has presented convincing data in support of his proposal that the term "postconcussion syndrome" be dropped. In view of the fact that little evidence exists for any relationship between cerebral contusion as evidenced by bloody cerebrospinal fluid and the common sequelae of head injury, it is also proposed that such a term be dropped. Denny-Brown<sup>2</sup> has used the term "post-traumatic cerebral syndrome." This is more acceptable than any term previously proposed because it does not restrict consideration to any specially assumed type of injury to the brain. It is suggested, however, that the wording of that term be revised to read "post-cerebral-traumatic syndrome."

The one conclusion which emerges from this study is that generalizations cannot be applied to a particular case. In various cases there may be great differences in the causes of the sequelae. In a particular case the sequelae are likely to be the resultant of various factors rather than of a particular one.

#### SUMMARY

One hundred and one civilians with acute head injuries were subjected to intensive study of multiple factors in the pretraumatic and the post-traumatic personality status. A clinical quantitated estimate was made of the degree of each of these specific personality factors. With such a method a multidimensional perspective of each patient was obtained, by which it was possible to quantitate changes, if any, in personality following head injury.

In addition, all patients were given categorical classifications of the pretraumatic personality (normal, psychoneurotic, psychovariant and psychopathic).

Correlations were made with the nature and estimated severity of the acute cerebral trauma and with various potentially complicating factors, such as associated bodily injuries and various possible sources of psychologic stress (litigation, occupation and financial and marital difficulties).

It was found that in a number of patients neurotic symptoms appeared for the first time after head injury. In most patients psycho-

logic changes following head injury became most manifest shortly after discharge from the hospital and were at a maximum three to six weeks after discharge. The duration of post-traumatic symptoms varied but in general they were substantially receding at the end of three months. However, approximately 50 per cent of the patients showed some persistence of symptoms at six months, and approximately 15 per cent had symptoms which persisted a year or longer. The duration of incapacity for work paralleled the persistence of psychologic symptoms, but most patients returned to work before they were entirely free of symptoms.

Patients with pretraumatic psychoneurotic personalities showed a greater proportion of post-traumatic psychiatric symptoms than did patients in other groups. However, the patients with pretraumatic normal personalities were closer to the psychoneurotic patients than were members of other groups.

There was no close correlation between the severity of the acute injury of the brain and the severity of the sequelae.

There was high correlation between the existence of persistent complicating psychosocial factors, such as continuing compensation, pending litigation, occupational stresses and persistent associated bodily injuries, and the severity and persistence of psychiatric sequelae.

No correlations were found which would permit the ascription of psychiatric sequelae to one particular cause or group of causes. The psychiatric sequelae in an individual case were usually the resultant of various factors. The etiologic factors in the psychiatric sequelae in a particular case depended on specific factors in that case.

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# EFFECTS OF DENERVATION ON FASCICULATIONS IN HUMAN MUSCLE

Relation of Fibrillations to Fasciculations

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AND

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PHILADELPHIA

**I**N A previous communication<sup>1</sup> evidence was presented to the effect that fasciculations in voluntary muscle have their site of origin not in the anterior horn cell but at the myoneural junction. This evidence consisted of the demonstration of continued fasciculations during pharmacologic block of the appropriate peripheral nerves or nerve roots and of the alteration of the frequency of fasciculations by drugs acting at the myoneural junction.

Subsequently, Denny-Brown<sup>2</sup> mentioned the disadvantages of pharmacologic block and indicated that this type of block could not be considered absolute in the physiologic sense, for the drug employed need not affect all the fibers in a given nerve to the same degree nor could the interference with transmission of sensory or voluntary motor stimuli permit one to conclude that all impulses were blocked.

For these reasons, confirmatory evidence for our previous premise regarding the site of origin of fasciculations was sought. It was thought that this could be supplied by observations on muscles denervated by section of the motor nerve supply. It was also hoped that by these studies some light might be thrown on the confusing problem of the relationship, or lack of relationship, between fasciculations and fibrillations.

## METHODS

The experiments were performed on 2 patients with severe amyotrophic lateral sclerosis. Both patients were disabled to such an extent by their disease process that nerve section did not materially increase their disability. In one experiment the left axillary nerve was sectioned in a patient with severe atrophy, weakness and fasciculations of the muscles of both shoulder girdles. In the second experiment the right femoral nerve was sectioned in a bedridden patient with pronounced atrophy, weakness and fasciculations of the muscles of all four extremities. This patient was also the subject of the third experiment, in which the left femoral nerve was sectioned. All nerve sections were performed with the usual surgical

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From the Department of Neurology of Jefferson Medical College

1 Forster, F M, and Alpers, B J. The Site of Origin of Fasciculations in Voluntary Muscle, *Arch Neurol & Psychiat* 51:264 (March) 1944

2 Denny-Brown, D. Personal communication to the authors

precautions. In addition to simple sectioning, a portion of each nerve approximately 2 cm in length was removed. The cut ends of the nerves were not sutured. All the wounds healed uneventfully.

Fasciculations were recorded electrically by means of a three channel, condenser-coupled amplifier with ink-writing oscillograph (Grass). The electrodes consisted of coaxial needle electrodes and of pairs of single needles placed at a distance of 0.5 cm. In deriving conclusions, only records from the coaxial needle electrodes were considered. Readings were taken prior to and after section of the peripheral nerves and from control muscles in other extremities, as well as from the muscles concerned in the present study. Electrode placements were through tattoo marks placed in the skin so that variation of placement might be reduced to a minimum. In each reading the number of fasciculations appearing in ten minutes was recorded. When neostigmine was given, the dose employed was 15 mg, and the intramuscular route was chosen. Atropine sulfate, 13 mg, was administered simultaneously with the neostigmine.

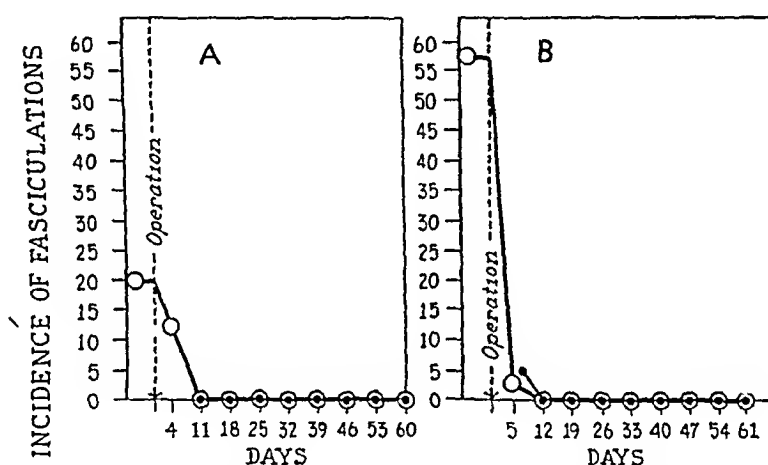


Fig 1—Effects of denervation on incidence of fasciculations, as observed at weekly intervals. In experiment 1 (*A*), on the fourth day after section of the axillary nerve the incidence of spontaneous fasciculations in the deltoid muscle had decreased, and on the eleventh and on all subsequent days fasciculations were absent. Neostigmine induced no fasciculations. In experiment 2 (*B*) five days after section of the femoral nerve fasciculations in the quadriceps muscle decreased and were absent on the twelfth and on subsequent days. Neostigmine was without effect after the twelfth day.

In this figure, and in figure 2, the line with large, hollow circles indicates values for spontaneous fasciculations, and the line with small, solid circles, the values for neostigmine-induced fasciculations.

## RESULTS

In the control observations, in experiment 1 (fig 1 *A*), an average of 20 fasciculations occurred in a single motor unit in the course of ten minutes. Four days after denervation the incidence was 15 fasciculations during a ten minute period. Beginning with the eleventh day, no spontaneous fasciculations appeared, nor did the administration of neostigmine produce fasciculations in the denervated deltoid muscle, despite the marked increase present in the nondenervated muscles. In experiment 2 (fig 1 *B*) the control observations indicated an average

frequency of fasciculations of between 55 and 60 in a given motor unit during a ten minute period. Five days after denervation only 3 spontaneous fasciculations occurred, and neostigmine given intramuscularly induced only 6 fasciculations in an identical interval of time. On the twelfth day and at each succeeding seventh day reading, neither spontaneous nor neostigmine-induced fasciculations appeared in the denervated quadriceps femoris muscle, while a marked increase of fasciculations was present in the nondenervated fasciculating muscles.

These two experiments were conducted simultaneously and were part of a series of long term studies of these patients at weekly intervals. It was apparent from these studies that fasciculations were not immediately abolished by denervation and that a later disappearance of this muscle phenomenon took place. It was obviously necessary to study the problem at shorter intervals.

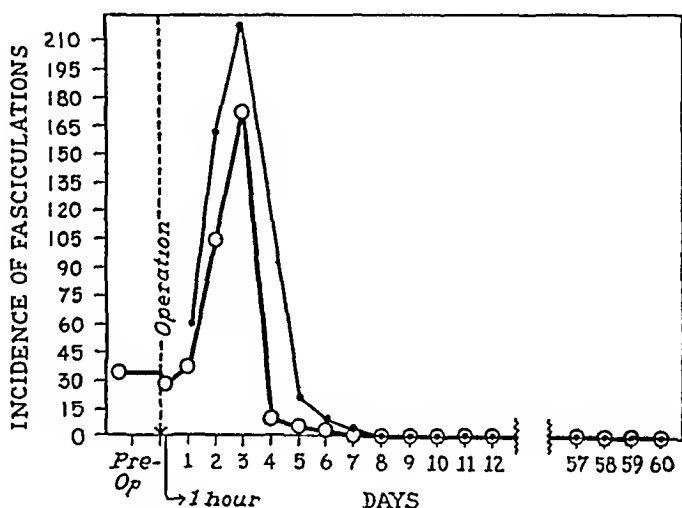


Fig 2—Effects of denervation on incidence of fasciculations, as observed at daily intervals in experiment 3. There was a transient increase of fasciculations in the quadriceps femoris muscle after section of the femoral nerve and absence of spontaneous and neostigmine-induced fasciculations on the eighth and on all subsequent days. The break in the base line indicates that no fasciculations were recorded between the twelfth and the fifty-seventh day.

In experiment 3 (fig 2), after section of the left femoral nerve, daily observations were made for a period of sixty days. There was a striking increase in the incidence of both spontaneous and induced fasciculations on the second and third postoperative days, followed by complete cessation of both spontaneous and induced fasciculations from the seventh day after sectioning.

#### CONCLUSIONS

*Effect of Denervation*—In three separate experiments the denervation of fasciculating human skeletal muscle failed to produce immediate

disappearance of fasciculations In the single experiment in which daily recordings were made an increase in the number of fasciculations was noted on the second and third days after nerve section, and both spontaneous and neostigmine-induced fasciculations failed to appear after the seventh day following denervation In the other two experiments, with observations at weekly intervals, fasciculations were present on the fourth and fifth days after denervation but could not be elicited on the eleventh and twelfth days or on subsequent days following nerve section

The presence of fasciculations during the first seven days after nerve section confirms the opinions derived from the previously reported observations on pharmacologic block of the nerve supply of fasciculating muscle The very presence of fasciculations in muscle after section of the motor nerve supply of that muscle demonstrates conclusively, that the anterior horn cell cannot be the site of origin of fasciculations in muscle, as there is no longer any continuity of conduction pathways between the anterior horn cell and the myoneural junction There remains as the possible site of origin only the distal portion of the nerve, the myoneural junction and the muscle itself Since it is unlikely that the nerve fibers themselves could give rise to impulses producing these muscle fiber contractions and since, as was demonstrated in the previous observations,<sup>1</sup> the frequency of fasciculations is influenced by drugs acting at the myoneural junction, the logical deduction is that fasciculations originate in this region

In these experiments there could be no question of the complete interruption of the motor nerve supply of the denervated muscles Muscles chosen for study were such that a single nerve contained their entire motor nerve supply Not only were these nerves sectioned, but a considerable portion of the nerve trunk was excised so that the separation of distal and proximal ends would be greater than that produced by simple section Thus, any possibility, however slight, of nerve regeneration during the course of the experiments was obviated The use of coaxial grounded needles insured against the possibility of pick-up from surrounding, nondenervated muscles In addition to this, it was possible visually to observe gross fasciculations of the denervated deltoid and quadriceps femoris muscles The continued presence of fasciculations for a period of days after denervation confirms the previous deductions from pharmacologic nerve block and hence indicates the validity of the use of spinal anesthesia or of nerve block in studying this problem

The ultimate disappearance of fasciculations in denervated muscles raises a vexing point, and one which requires a further consideration of differences and relationships between fasciculations and fibrillations.



*Fibrillations Versus Fasciculations*—In many respects the differences between fasciculations and fibrillations are not decisive. Fibrillations are fine, continuous, tremor-like contractions, visible in strong reflected light on the surface of exposed denervated muscle. Fasciculations are grosse<sup>1</sup> contractions, apparent through the intact skin, and appear classically in association with disease of the anterior horn cell. Fibrillations are considered to be contractions of a part of or an entire muscle fiber. Fasciculations are considered to be the contraction of a group of muscle fibers, a single motor unit. The differentiation between these two types of involuntary muscular contraction, as cited, was clarified by Denny-Brown and Pennybacker,<sup>3</sup> who concluded that fibrillations arose at the myoneural junction and inferred that fasciculations arose from the anterior horn cells. However, even they found occasionally in their experiments that fibrillations approached fasciculations in their characteristics. Tower,<sup>4</sup> in her review, concluded that it is uncertain whether a sharp distinction exists between the two phenomena and advocated the utilization of such critical procedures as nerve block to differentiate further between the two states.

Among neurologists there is no clear differentiation between fibrillations and fasciculations, and, indeed, many clinicians and some physiologists employ the terms interchangeably. On the surface the problem would seem to be quite simple, in view of the previously outlined differences, especially since fibrillations occur only after denervation and fasciculations appear in the presence of disease of the anterior horn cells. However, both progressive muscular atrophy and amyotrophic lateral sclerosis are associated not only with diseased neurons of the anterior horn cells but also with a paucity of cells, thus producing essentially a denervation of the corresponding motor units. Viewed from this standpoint, the apparently different etiologic origin of the two phenomena loses much of its importance. The similar site of origin, the myoneural junction, of the two phenomena also tends to lessen the differences between them.

Fibrillations appear in denervated animal muscle in varying periods of from two to eight days after denervation, the longer time intervals occurring with the higher animals. Feinstein, Pattle and Weddell<sup>5</sup> found in a single experiment that it required sixteen days for the development of fibrillations in denervated human muscle. Fasciculations, according to our observations, disappear in human muscle approximately

3 Denny-Brown, D., and Pennybacker, J. B. Fibrillation and Fasciculation in Voluntary Muscle, *Brain* **61** 311, 1948.

4 Tower, S. The Reaction of Muscle to Denervation, *Physiol Rev* **19** 1, 1939.

5 Feinstein, B., Pattle, R. E., and Weddell, G., Metabolic Factors Affecting Fibrillation in Denervated Muscle, *J Neurol, Neurosurg & Psychiat* **8** 1, 1945.

seven days after denervation, while fibrillations appear at a somewhat later date and are permanent. The possibility immediately arises that fasciculations may be multiple, simultaneous fibrillations occurring in the same motor unit. Since fasciculations induced by neostigmine are known to yield antidromic impulses,<sup>6</sup> presumably from the myoneural junction, and since antidromic impulses have been described from peripheral stimulation of a motor nerve, it is conceivable that such impulses could exert a synchronizing effect on the muscle fibrils served by a single motoneuron axon. This could be accomplished either by the effect of antidromic impulses on the motoneuron in the anterior horn cell or by means of an axon reflex, thus not requiring the mediation of the anterior horn cell. In view of the persistence of fasciculations for some time after denervation, antidromic impulses could be effective only as part of an axon reflex. The pronounced decrease in the incidence of fasciculations occurring from the fourth to the fifth day after denervation corresponds well with the anatomic changes occurring in the axons of the peripheral stump of a sectioned nerve. At this stage of denervation the axons have become degenerated to a degree that segmentation occurs, together with inclusion of fragments of the axon with fragments of myelin. In other words, by the time fasciculations disappear in denervated muscle it is unlikely that the peripheral stump of the nerve retains the ability to conduct impulses from the myoneural junction.

The anatomic changes in denervated muscle cannot be correlated temporally with the disappearance of fasciculations. Alterations of muscle striations, sole plate granules and frankly degenerative changes occur much later, and, while subsarcolemmal nuclei show alterations early in the course of denervation, it is difficult to conceive of these alterations having any relevant bearing on the incidence of fasciculations. The determination of chemical alterations in denervated muscle has of necessity been on experimental animals. These studies<sup>4</sup> indicate that within the period of disappearance of fasciculations there occur an increase in calcium and phosphoric acid and a decrease in glycogen, potassium and phosphocreatine. These chemical alterations suggest a biochemical origin of the fasciculations, and the changes in potassium, coupled with the known increase of fasciculations produced by neostigmine indicate that synthesis and destruction of acetylcholine may be concerned with the induction of fasciculations at the myoneural junction.

In experiment 3 the increase of fasciculations during the second and third days after denervation requires further investigation. This was not noted in the other experiments, possibly as a result of too infrequent readings.

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6 Masland, R. L., and Wigton, R. S. Nerve Activity Accompanying Fasciculations Produced by Prostigmin, *J. Neurophysiol.* **3** 269, 1940.

## SUMMARY

Fasciculations do not arise at the anterior horn cell, since they are present for a time after denervation of the fasciculating muscle. Fasciculations, like fibrillations, originate at the myoneural junction. Fasciculations and fibrillations probably represent the same phenomenon, the only difference being that fasciculations are synchronized fibrillations occurring in the same motor unit. The decrease of fasciculations about four days after denervation correlates with the anatomic changes in the peripheral nerve stump. Fibrillations are probably synchronized into fasciculations by antidromic impulses from the myoneural junction and firing in axon reflex fashion. The disappearance of fasciculations is due to the destruction of the synchronizing pathway when the peripheral stump degenerates.

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## DISCUSSION

DR RICHARD MASLAND, Philadelphia. It is important to emphasize the distinction between fibrillation and fasciculation. In fibrillation the individual muscle fibers contract independently. In fasciculation there is a synchronized discharge of a group of muscle fibers. There is every reason to believe that this synchronization is due to neural activity and represents the response of a motor unit to a nerve impulse.

It has been shown that in the case of the fascicular twitch which follows the administration of neostigmine there is a nerve impulse associated with the contraction. This impulse may arise either through antidromic musculoneural transmission or by direct stimulation of the nerve ending sensitized by the drug (Eccles, J. C., Katz, B., and Kuffler, S. W. *J. Neurophysiol.* 5:211, 1942). When the nerve ending is stimulated, an antidromic impulse is set up, there is an axon reflex, and a motor unit discharge results.

There is a striking similarity between the "neostigmine twitch" and the fasciculation of anterior horn cell disease. Both are inhibited by small doses of curare. The experiments just concluded indicate that each arises at the nerve ending. It is my belief that in each instance the fundamental element is an abnormal excitability of the nerve ending.

In attempting to explain the fact just demonstrated that although the disease is in the anterior horn cell the twitch arises at the nerve ending, it is important to bear in mind that the anterior horn cell includes not only the cell body but the peripheral nerve, which is its axon, and the nerve ending. It is not remarkable, therefore, to discover that a disease which is demonstrated pathologically in the cell body within the spinal cord produces striking physiologic changes in the entire cell. These manifest themselves as an alteration in excitability at one of the more highly specialized portions of the neuron—the nerve ending.

DR RICHARD MASLAND, Philadelphia. In reply to Dr. Alper's question, Eccles has expressed the opinion that the increased irritability of the nerve ending observed with neostigmine poisoning may be due to prolonged negativity. In view of the striking similarity between the twitch seen with such diseases as amyotrophic lateral sclerosis and the "neostigmine twitch," it is not unreasonable to postulate that the same factor is responsible for both.

DR FREDERIC H. LEWEY, Philadelphia. The question of fibrillations or fasciculations is important also from the clinical point of view. A review of the textbooks shows it to be almost an axiom that "fibrillation" is characteristic of a

lesion of the anterior horn cell, in contrast to one of the peripheral nerve. Oscillographic records show that the completely denervated muscle "fibrillates." This is not visible clinically. The first sign of beginning reinnervation of a muscle is the appearance of not yet synchronized, spread potentials, which are now called "fasciculations"! They are visible clinically as what were formerly called fibrillations. No voluntary motion is possible at that stage. The last stage of muscle reinnervation is characterized by the appearance of synchronized action potentials, i. e., spikes, accompanied with the return of voluntary movements. This experience gained from patients with peripheral nerve injuries corresponds to the observations of the authors, with the restriction that in diseases such as spinal progressive muscular dystrophy some units may be diseased and others still functioning well.

DR FRANCIS M. FORSTER, Philadelphia. Our use of the term anterior horn cell should be clarified, for by that term we referred to the cell body and its nucleus, and not specifically to the axonal terminations. The experimental data presented this evening indicate definitely that the impulses giving rise to fasciculations did not originate from the portions of the cells in the ventral horns of the spinal cord. Fundamentally, I do not believe there is any real difference of opinion between ourselves and Dr Masland. Our studies did not include patients with myopathies. However, the myopathies are not always sharply delineated, and the occurrence of clinical or pathologic evidence of involvement of the cord with the myopathies is by no means rare.

# TOXICITY OF QUINACRINE (ATABRINE) FOR THE CENTRAL NERVOUS SYSTEM

## III An Experimental Study on Human Subjects

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AND

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A METHOD of detecting and measuring the toxic effects of drugs on cerebation and its use in a preliminary investigation of the toxicity of quinacrine (atabrine) are presented. The procedure is simple and consists in principle in comparing the intellectual functioning of subjects while taking the drug and when free of the drug. Groups of subjects receiving different doses of quinacrine hydrochloride and with varying serum levels of the drug were tested to gain an approximate estimate of the dose which tends to be toxic for human subjects.

The study was undertaken when it was observed, during the treatment of many thousands of patients for malaria, that the most serious toxic effect of quinacrine was the occurrence of toxic psychoses. This complication was seen most often after excessive doses. Massive quinacrine therapy had been instituted on the island on which we were stationed to determine whether the production and maintenance of a high quinacrine level in the serum would check the recurrence of tertian malaria. The sole serious limitation to the quantity of quinacrine which could be given appeared to be the relationship between the rapidity of administration of large doses and the occurrence of confusion or overt psychoses. As the treatment by massive dosage brought little, if any, benefit, the experiment was abandoned. However, the experience indicated that as the important toxic effect of quinacrine was on the central nervous system, the limitations of dosage should be determined in terms of the effect of the drug on the central nervous system. A means was therefore sought which would permit the measurement of the effects of the drug on mental functioning.

It is well to clarify the meaning of toxicity as applied to quinacrine. The risk to be taken in the use of a drug is proportionate to the benefits to be derived. The toxic dose cannot be determined according to fixed

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\* On leave of absence from the Phipps Psychiatric Clinic

Originally submitted for publication to the Office of the Surgeon General in September 1944

standards. If massive dosage of quinacrine decreased the rate of recurrence of tertian malaria markedly, the risk of an occasional quinacrine psychosis might well be considered worth while. The balancing of an optimal therapeutic dosage would then be a difficult matter. As it now appears that heavy dosage is of little benefit, the problem is not difficult. The dose is to be maintained below that which will produce toxic effects. The determination of toxic levels of the drug, which is the purpose of this study, would be a matter of only pharmacologic interest if it were not for the problem of the toxic psychoses.

Quinacrine psychoses have been reported by a number of observers. Experiences on this island with 28 cases of toxic psychosis<sup>1</sup> and 7 cases of convulsive seizures<sup>2</sup> due to quinacrine among approximately 30,000 patients treated for malaria have been reported in previous papers. Psychoses were infrequent when conventional therapy (2.1 or 2.8 Gm of quinacrine hydrochloride in seven days) was used but increased in frequency when massive therapy (1.4 Gm in twenty-four hours, 3.8 or 4.8 Gm in seven days, and so on) was employed. With cessation of heavy dosage, quinacrine psychoses again became a rarity, although the number of patients treated remained unaltered. It was noted that, in addition to the patients with frank psychoses, a fair number of the men who received the large amounts of quinacrine complained of feeling confused or intoxicated. Confusion is basic to the toxic psychoses and connotes impairment of mental functioning. It was believed that if the mentation of some patients were sufficiently disturbed by the quinacrine to produce confusion that was perceptible, either objectively or subjectively, the utilization of refined means of testing would uncover lesser degrees of impairment in a larger proportion of the patients.

It happened that 2 patients who became psychotic under massive quinacrine therapy had been given intelligence tests a day or two before they had the onset of psychosis, but after they had taken a large quantity of quinacrine. The severity of the mental deficiency that existed in both patients was estimated erroneously, for the patients showed a significant increase in their mental ages when retested after recovery from the psychosis and after quinacrine had been withdrawn for some time. For 1 of the patients the score on the Stanford-Binet test shifted from a mental age of  $6\frac{9}{12}$  years to one of  $9\frac{3}{12}$  years, and for the other, from a mental age of  $9\frac{9}{12}$  years to one of  $11\frac{8}{12}$  years, and the score on the Kohs block test given the second patient shifted from a mental age of 6 years to  $10\frac{11}{12}$  years. The presence of impaired intellectual functioning prior to the onset of the psychoses in these patients sug-

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1 Newell, H. W., and Lidz, T. The Toxicity of Atabrine to the Central Nervous System. I. Toxic Psychoses, *Am J Psychiat*, to be published.

2 Newell, H. W., and Lidz, T. The Toxicity of Atabrine to the Central Nervous System. II. Convulsions, *Am J Psychiat*, to be published.

gested that transient impairments due to subclinical confusion might well be found in other patients receiving massive doses of quinacrine

#### SELECTION OF THE TEST PROCEDURE

The comparison of intellectual functions in a subject at any two times may be carried out in a number of ways, and emphasis may be placed on various functions of the intellect. There are limitations in the choice of the procedure which must be considered. It is realized from the study of deteriorations following structural damage to the brain that such changes, particularly when of recent origin, are not always apparent. Some tests of mental capacity may fail to reveal the defect, for the patient retains information, habitual modes of thinking and patterns of behavior which had been acquired when the intellect was intact. Learned material which can be given without complicated reflective or synthetic thinking may remain at the disposal of the patient. Therefore, such methods of measuring intelligence as the Binet test, which measures to a large extent what the subject has learned by means of his intelligence, are unsuited to the study of deteriorations. It is necessary to test the ability for active mentation at the moment, utilizing a method which permits a minimum of reliance on knowledge and behavioral patterns acquired in the past. For group studies, it is necessary to select a procedure which yields numerical data that can be utilized statistically.

The choice of a suitable procedure has been discussed in detail by Lidz, Gay and Tietze,<sup>3</sup> in an article on the application of the Kohs block test to the study of organic deficit states. The Kohs block test seems equally advantageous for the study of transitory impairment of the intellect. It is singularly free from the influence of past experience, it is a well standardized and highly reliable procedure, suited to adult testing, it is well graded and measures a wide range of intelligence levels, retesting with the same procedure does not produce significant alterations in the score, and there is little room for subjective error in the results, which are scored in numerical terms. Although several other procedures were utilized at the start of the experiment, particularly memory tests, it was found that whenever significant results were obtained they were also to be noted in the Kohs block test. The discussion of the experimental results will therefore be limited to this test.

The nature of the Kohs block test and the method of administration will be outlined briefly. A complete discussion of the test has been presented by Kohs,<sup>4</sup> but the procedure has been modified slightly

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3 Lidz, T., Gay, J. R., and Tietze, C. Intelligence in Cerebral Deficit States and Schizophrenia Measured by Kohs Block Test, *Arch Neurol & Psychiat* 48:568 (Oct) 1942

4 Kohs, S. C. Intelligence Measurement, New York, The Macmillan Company, 1923

The test material consists of 16 identical 1 inch (2.54 cm) color cubes and 17 standardized designs of graded complexity drawn on separate cards to a 1-4 scale. Each cube has four solidly colored sides—blue, red, white and yellow, a fifth side is divided diagonally into red and white, and a sixth, into blue and yellow. It is explained that the 16 cubes are identical, and the various sides are pointed out. A simple sample design is presented to the subject, who is requested to reproduce the pattern with the upper surfaces of the cubes. The subject is given all 16 blocks. It is explained that only 4 cubes are needed to form the simple pattern, but more will be necessary for some designs. The method of forming the sample pattern is demonstrated if necessary. The subject is then requested to make the first design as rapidly as possible and is then offered one design after another until failure occurs on three successive patterns. If the subject does not realize that more than 4 blocks are needed to form the tenth design, he is told. The time permitted for the completion of each pattern is found on the card, but precise time is recorded, as bonus scores are given for rapid completions.

The scoring and calculations of the mental age are made according to the tables of Kohs,<sup>4</sup> but the number of moves made in the completion of a pattern is not taken into consideration, as many workers have found it to be a complicating factor that does not increase the accuracy of the procedure appreciably. A perfect score is equivalent to a mental age rating of 20 years, and the lower limit, inability to complete the simplest design, indicates a mental age of less than 5½ years.

As the test was to be given twice to the same subject, two sets of design cards were used to minimize the learning factor. The second set consisted of the same designs but with the color scheme reversed. The red and white patterns were made blue and yellow and vice versa except for the seventeenth design, which would be simplified by reversal of the color scheme. The first control group was divided in half, and each half was tested with opposite sets of patterns and retested with the other set. No appreciable difference between the sets of patterns was found.

The results of each test were calculated in years of mental age, and the difference between the two tests was calculated in months of mental age.

#### PLAN OF THE EXPERIMENT

The simplest and most satisfactory approach would be to determine the mental ages of a group of subjects with the Kohs block test, administer quinacrine and retest with the Kohs block test after a given amount of the drug had been taken or a definite serum quinacrine level had been attained. A fall in the mental age on the retest of more than 1 year or 18 months would be an indication of impaired mentation, as subjects tend to gain a higher score on the retest and rarely show a decline in score of as much as 18 months. The study was carried out under conditions which imposed limitations that complicated the procedure.

It did not appear wise or practicable to administer heavy doses of quinacrine to volunteers. The experimental subjects were patients with recurrences of tertian malaria who received the quinacrine therapeutically. It was necessary, therefore, to administer the first Kohs test when the patients were receiving the drug and to retest later, when the patient had ceased taking quinacrine and had been free



from the drug for some time. A pronounced increase in score would indicate that impairment existed when the first test was given.

Familiarity with the procedure, rather than elimination of the toxic agent, would then account for some of the improvement on the second test. The limitation was overcome and controlled by measuring the improvement shown by a group of normal subjects, persons who did not take the drug and did not have malaria. The presence of malaria constituted a second factor which might influence the results, for it was possible that the malaria might cause a transient impairment of mental functioning even though the subjects were afebrile and had recovered from the attack when tested. A second control group was established which was composed of patients who had malaria but who were treated with quinacrine in a dose which would be unlikely to have an effect on the central nervous system. Tests on the two control groups yielded similar results, indicating that the second group was not affected by the small dose of quinacrine, as will be seen later. The results of the testing of the experimental subjects were then analyzed by comparison with the data for the two control groups.

TABLE 1—*Scores on Kohs Block Tests for 30 Control Subjects Who Received No Quinacrine*

Number	Test Score *	Retest Score †	Difference in Score (Mo.)	Number	Test Score	Retest Score	Difference in Score (Mo.)
1	13.7	12.7	-12	16	12.8	14.3	+19
2	13	12.7	-5	17	16	17.8	+20
3	11.3	10.11	-4	18	13.5	15.3	+22
4	10.4	10.2	-2	19	18	19.10	+22
5	20			20	18	20	+24
6	20			21	14.2	16.6	+23
7	20			22	17.6	19.10	+28
8	19.3			23	13.11	16.4	+29
9	9.3	9.6	+3	24	15.9	18.2	+29
10	17.8	18	+4	25	14	16.8	+32
11	17.6	18	+6	26	12	14.11	+35
12	12.3	13.1	+10	27	16	18.11	+35
13	11.2	12	+10	28	16.6	20	+42
14	18.11	20	+13	29	11.4	14.11	+43
15	14.2	15.3	+13	30	15.5	19.8	+51

\* Mental age in this table, and in subsequent tables, is expressed in years and months.

† Patients were retested after an interval of seven days.

‡ Subjects who attained very high scores on the first test were not always retested.

A third limitation may have detracted slightly from the accuracy of the experimental results, but as the effect would be to minimize significant data rather than to exaggerate them, it is not of great importance. The need for hospital beds required that the retests be carried out as soon as possible. The subjects were retested one week after the cessation of quinacrine therapy, and there were indications that the effects of the drug had not disappeared completely by that time. A small group of subjects and controls were tested for a third time after an interval of one month to estimate the significance of the error.

The following groups of subjects were tested:

GROUP 1—This series consisted of 30 normal subjects. They were members of the hospital detachment who had never had malaria and had never received quinacrine. There was an interval of seven days between the two tests. The series formed the control showing the increase in the score due to familiarity when retesting was done after an interval of seven days. The results of the testing are shown in table 1. Ten subjects were retested a second time, a month after the first test was given.

GROUP 2—This series consisted of 27 patients who were treated for malaria with quinacrine hydrochloride, 0.1 Gm three times a day for seven days, a total of 2.1 Gm. The patients were tested on the seventh day of treatment and were retested after an interval of seven days. Serum quinacrine levels were obtained on 26 patients on the sixth, seventh, or eighth day.<sup>5</sup> The subjects were all afebrile, asymptomatic and ambulatory when tested. The series formed a control against the possibility that the malaria influenced mental functioning. The results of the testing are to be found in table 2.

GROUP 3—The series consisted of 31 patients who were treated for malaria with quinacrine hydrochloride according to a schedule of 0.3 Gm three times a day for three days, followed by a regimen of 0.2 Gm three times a day for three days, making a total dose of 4.5 Gm in six days. The patients were tested on the sixth day of treatment and were retested after an interval of seven days. Serum quinacrine levels were obtained on 29 patients some time between the fourth and the eighth day (23 patients on the fourth day). The patients were

TABLE 2—*Scores on Kohs Tests for Control Group of 27 Subjects Who Received 2.1 Gm of Quinacrine Hydrochloride in Seven Days*

Number	Test Score *	Retest Score †	Difference in Score, Mo	Serum Level, Micrograms per 100 Cc ‡	Number	Test Score	Retest Score	Difference in Score, Mo	Serum Level, Micrograms per 100 Cc
1	12.6	11.5	-1.3	3	15	14-10	16.4	+1.8	4
2	12.3	11.4	-1.1	7	16	12.7	14.3	+2.0	4
3	14.3	13.7	-.8	3	17	14.2	16	+2.2	4
4	14.11	14.7	-.4	3	18	11.11	13.11	+2.4	5
5	20			4	19	10.4	12.9	+2.9	3
6	19.8			5	20	13.2	15.7	+2.9	5
7	18			2	21	14.6	17	+3.0	3
8	18.2			1	22	11.6	14	+3.0	5
9	19.6			3	23	13.11	16.8	+3.3	8
10	17.10			6	24	8-10	11.9	+3.5	
11	19.8			5	25	10.6	19.6	+3.6	8
12	15.5	16.7	+1.4	5	26	16.7	19.8	+3.7	6
13	12	13.3	+1.5	10	27	15.7	19.3	+4.4	3
14	16.5	17.10	+1.7	7					

\* Patients were tested on the seventh day of treatment.

† Patients were retested after an interval of seven days.

‡ Serum levels were determined on the sixth, seventh or eighth day.

all asymptomatic and ambulatory when tested. This series forms the major experimental group. The results of the testing are to be found in table 3. Ten patients were retested a second time, one month after the initial test.

GROUP 4—A series of 10 patients form a subsidiary experimental group, as the experiment was interrupted before the series could be completed. The patients were treated with quinacrine hydrochloride, 0.1 Gm three times a day for twelve weeks. They were tested during the ninth week of treatment, after they had received approximately 1.7 Gm of quinacrine hydrochloride. Serum quinacrine levels were obtained at the time of testing. The patients were tested again two weeks after the termination of treatment, and five weeks after the first

<sup>5</sup> Determinations of the serum quinacrine level were provided by Capt Roger A. Lewis, Medical Corps, Army of the United States, and were made by his method, which has been well standardized (Lewis, R. A. J. Lab & Clin Med 29:1303 [Dec] 1944).

test was made. The series of tests was intended to determine whether large quantities of quinacrine given in a dosage which did not produce a very high serum level could cause toxic symptoms. The group is small and will not enter into consideration except as the data were used as a further check on the results.

TABLE 3—*Scores on Kohs Test for Experimental Group of 31 Subjects Who Received 4.5 Gm. of Quinacrine Hydrochloride in Six Days*

Number	Test Score *	Retest Score †	Difference in Score, Mo	Serum Level, Micrograms per 100 Cc ‡	Number	Test Score	Retest Score	Difference in Score, Mo	Serum Level, Micrograms per 100 Cc
1	11.6	10.6	-12	12	17	11.2	12.11	+21	23
2	14.4	13.9	-7	11	18	6	8	+24	20
3	19.3			15	19	11.2	13.5	+27	20
4	19			11	20	15.5	18	+31	20
5	10.5	10.7	+2	10	21	9.5	12	+31	25
6	19.8	20	+4	10	22	13.10	17.4	+42	20
7	10.9	11.0	+9	15	23	16	19.10	+46	18
8	17.9	20	+27	10	24	15.3	19.3	+48	18
9	12	14.6	+30	10	25	12.4	16.4	+48	30
10	12	14.9	+33	9	26	12.5	16.11	+54	18
11	11.6	15.6	+48	12	27	10.7	15.4	+57	20
12	11.1	10.8	-5	25	28	13.8	19.8	+72	20
13	9.5	9.10	+5	18	29	11.9	18	+75	28
14	12.2	12.10	+8	20	30	20			
15	19	19.8	+8	20	31	15.8	18.5	+33	
16	11.4	12.10	+18	20					

\* Patients were tested on the sixth day of treatment.

† Patients were retested after an interval of seven days.

‡ Serum levels were determined between the fourth and the eighth day (23 patients on the fourth day).

TABLE 4—*Scores on Kohs Test for Subsidiary Experimental Group Who Received 0.3 Gm. Quinacrine Hydrochloride Daily for Twelve Weeks*

Number	Test Score *	Retest Score †	Difference in Score, Months	Serum Level, Micrograms per 100 Cc ‡
1	12.7	11.3	-16	7
2	13.6	12.9	-9	15
3	19			11
4	14.3	14.5	+2	7
5	17.4	17.11	+4	6
6	16.7	17.6	+11	10
7	15.11	17.5	+18	9
8	14.10	16.7	+21	
9	10.6	12.4	+22	8
10	7.5	10	+31	6

\* Patients were tested during the ninth week of treatment.

† Patients were retested during the fourteenth week.

‡ Serum levels were determined during the ninth week.

obtained in the testing of the other groups of patients. The results are to be found in table 4.

In all groups, subjects who attained very high scores on the first test were not always retested, as it was apparent that no measurable deficit had resulted from the quinacrine therapy. The lapse in technic had no appreciable effect

except in group 2, in which the mean increase in mental age on the retest may be 1 to 2 months lower than it should be, an error without significance in the results of the study

#### ANALYSIS OF DATA

The experimental data concerned with the first three groups will first be examined on the basis of the dose of quinacrine and thereafter on the basis of the serum quinacrine levels

TABLE 5—Means for Scores Obtained by Three Groups of Subjects

	Mean Mental Age Test I, Yr	Mean Mental Age Test II, Yr	Mean Difference Between Tests, Mo
Group 1 (no quinacrine)	15.1	16.5	16.4
Group 2 (2.1 Gm quinacrine)	15.0	16.2	14.7
Group 3 (4.5 Gm quinacrine)	13.4	15.5	25.1

The means for the scores obtained on the tests by each group of subjects are given in table 5

It is seen that the means for groups 1 and 2 are practically identical. The means for group 3 differ from those for the other two groups, the scores being lower on the tests and the difference between the scores on the two tests being greater. The difference appears suggestive but cannot be considered of statistical significance. However, a significant statistical variation between the mean differences in the scores could not be anticipated unless a large majority of the subjects who received 4.5 Gm of quinacrine hydrochloride had shown a pronounced toxic effect from the drug. An analysis of the distribution of the scores in the three groups yields more interesting information.

Chart 1 shows the distribution of the scores obtained on the two tests by the subjects in groups 1 and 2. The chart is a scatter graph of the mental age levels obtained on the first test plotted against the mental age levels obtained on the second test. The scatters for the two groups are almost identical. Chart 2 shows the scatter of the mental ages on the test and on the retest obtained by the subjects of group 3. The tendency toward a greater increase in the mental age on the retest in group 3 than in groups 1 and 2 is apparent. Whereas chart 1, combining the values for 57 patients in groups 1 and 2, shows only 1 subject with an increase in mental age of 4 years or more on the retest, 7 of the 31 patients in group 3 showed an increase of 4 years or more.

The differences in the groups can be seen more easily from the study of chart 3. This chart is a cumulative frequency graph which shows the percentage of patients in each of the three groups that improved up to any given number of months on the retest. The curves for the first two groups, like the means and the scatter, are remarkably similar, indicating that the presence of malaria and the administration of 2.1 Gm of quin-

acrine hydrochloride had no effect on the mental functioning, at least as measured by the technic. The curve for the patients given 4.5 Gm of quinacrine hydrochloride differs. Not only do the values for some patients fall outside the limits of the curves for group 1 and group 2, but there is a generalized shift. The differences are summarized in table 6.

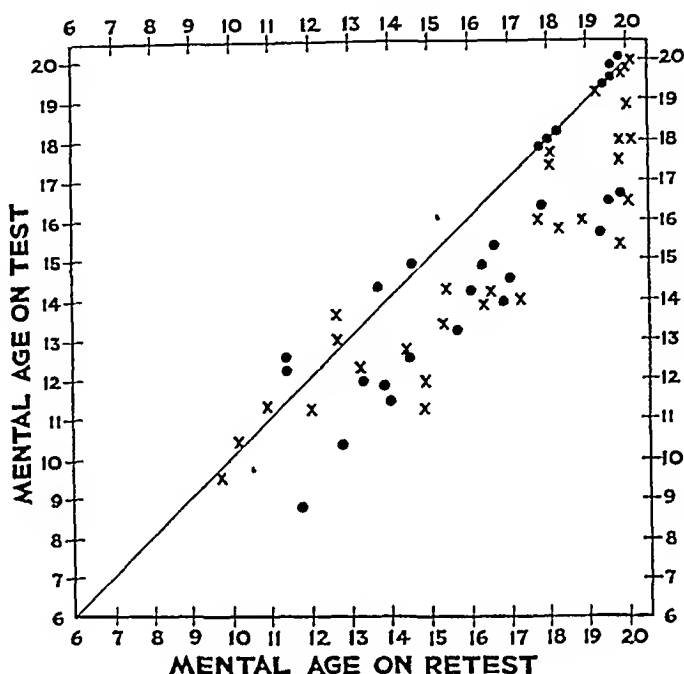


Chart 1—Correlation of mental ages obtained on Kohs block test and on a retest after seven days for group 1 (30 subjects, normal controls) and for group 2 (27 subjects given 2.1 Gm of quinacrine hydrochloride).

The values for the controls are shown by crosses, those for the patients given quinacrine, by solid circles.

TABLE 6—Distribution of Improved Scores for Three Groups of Subjects

Increase in Score (Months) on Retest of	Group 1 No Quinacrine, Per Cent	Group 2 2.1 Gm of Quinacrine, Per Cent	Group 3 4.5 Gm of Quinacrine, Per Cent
16 or more	50	48	61
24 or more	37	37	55
30 or more	20	26	45
36 or more	10	11	29
42 or more	10	4	29
48 or more	3	0	23
54 or more	0	0	13
60 or more	0	0	6

An improvement in the mental age of 48 months or more on the retest is seen to be decidedly unusual in the controls, whereas 23 per cent, or 7 subjects, who received 4.5 Gm of quinacrine hydrochloride showed such improvement, indicating that it is extremely likely that the quinacrine had impaired their mentation when they were first tested.

The higher percentage of subjects in group 3 that showed large discrepancies in the results of the two tests suggests that a large proportion of the group experienced some impairment due to the drug. Group 3 is obviously not a pure group, that is, some subjects seemed to have suffered from the toxicity of the quinacrine and others not. This might be anticipated, as it was apparent clinically that the dose could not be higher than that bordering on the toxic.

If the hypothesis is accepted tentatively that the tests indicate that a dose of 4.5 Gm affected some subjects and not others, several explanations may be offered. There may have been differences in absorption or excretion, with variations in serum levels, or differences in individual sensitivity, or other factors, such as spinal fluid levels, may have

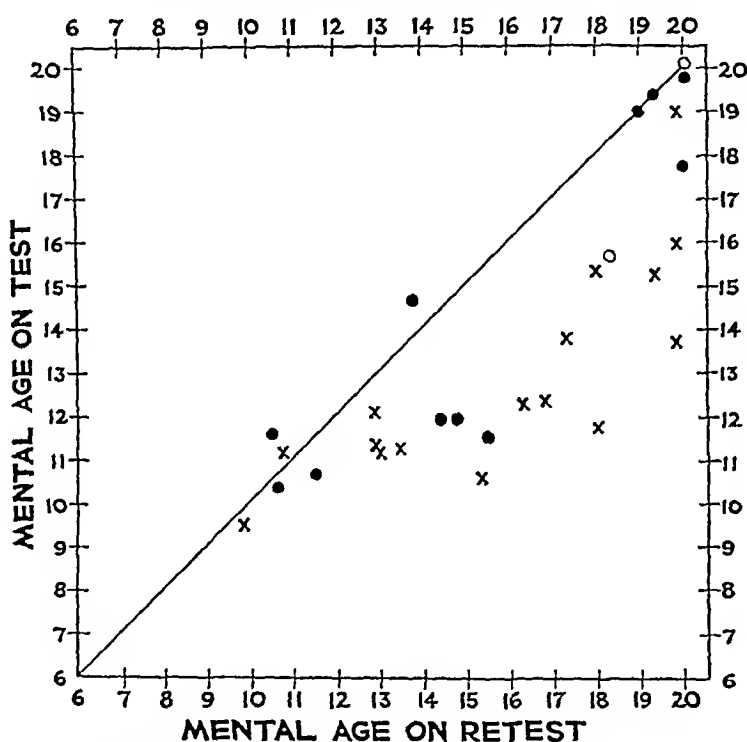


Chart 2—Correlation of mental ages on Kohs block test for group 3 (31 subjects) tested on the sixth day of treatment with 4.5 Gm of quinacrine hydrochloride and retested after seven days. The group is subdivided into subjects with high (18 micrograms per hundred cubic centimeters or more) and subjects with low (less than 18 micrograms per hundred cubic centimeters) serum quinacrine levels.

The values for the subgroup with higher serum quinacrine levels are shown by crosses, the values for the subgroup with lower serum quinacrine levels, by solid circles, and no determination of the serum quinacrine level is shown by a hollow circle.

to be taken into consideration. Analysis of the serum levels not only gives further information but tends to confirm the efficiency of the technic.

#### ANALYSIS OF DATA ACCORDING TO SERUM LEVELS

The compilation of data according to the quinacrine dose is an arbitrary procedure which is based on the knowledge, gained from a large

group of patients, that given schedules of therapy tend to produce serum quinacrine levels within certain limits. There is considerable variation in the serum levels in different subjects under the same regimen of treatment. It seems well to attempt to correlate the results of the mental testing with the measure of the toxic agent in the circulation.

Serum quinacrine levels were obtained on 26 of the 27 subjects in group 2 on the sixth, seventh or eighth day. It is known that there is little variation in serum levels during the last days of the course of treatment. The serum levels varied from 1 microgram (0.001 mg) to 10 micrograms (0.010 mg) per hundred cubic centimeters, with a mean level of 4.7 micrograms (0.0047 mg) per hundred cubic centimeters. As the results of the mental tests showed no toxic effect, it is highly

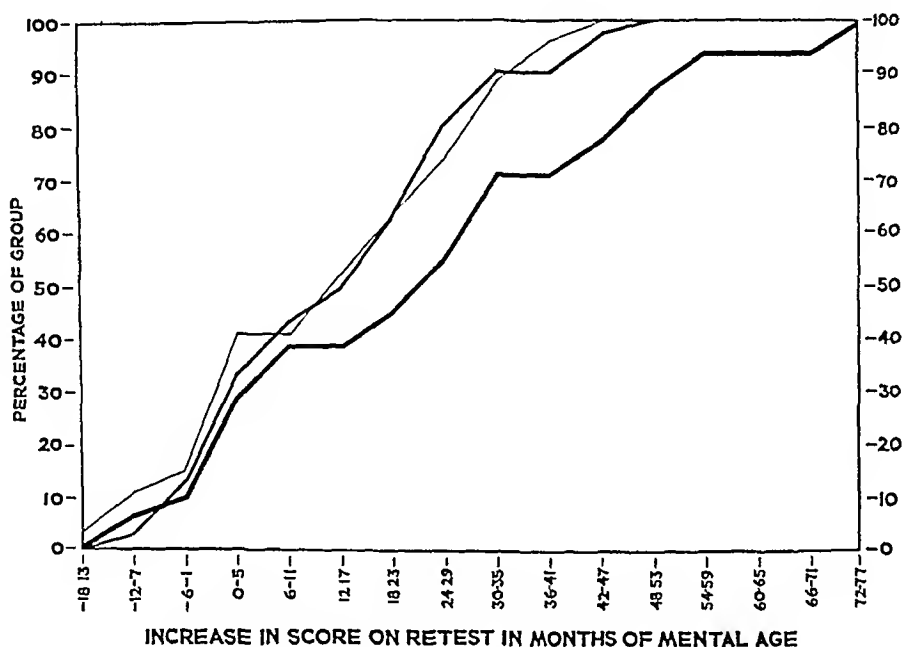


Chart 3—Cumulative frequency graphs comparing the mental age scores for group 1 (normal controls), group 2 (patients receiving 21 Gm of quinacrine hydrochloride) and group 3 (patients receiving 45 Gm of quinacrine hydrochloride). These curves show the percentages of subjects in each group who showed improvement up to any given number of months of mental age on the retest. The greater the improvement on the retest, the more likely that impairment existed when the first test was given.

The curve for group 1 is shown by a medium heavy line, the curve for group 2, by a light line, and the curve for group 3, by a heavy line.

probable that these levels are not toxic to human subjects. A further check was made by dividing the group into upper and lower halves, 13 patients having serum levels above the mean and 13 patients below. The mean increment in score between the tests for the 26 subjects was 13.9 months. The 13 patients with serum levels below 4.7 micrograms per hundred cubic centimeters had a mean increase of 10.6 months, whereas the 13 patients with the higher serum levels had a mean increase

of 17.2 months on the retest. Although this may indicate that the patients with the higher serum quinacrine levels may have had a slight toxic effect from the drug, the difference is well within the limits of experimental error. The mean increase in the score of 17.2 months is approximately the same as that shown by the controls in group 1.

Serum quinacrine levels were obtained on 29 of the 31 subjects in group 3, who had received 4.5 Gm of quinacrine hydrochloride. The levels were obtained between the fourth and the eighth day, for 23 of the 29 patients on the fourth day. Although these data are not as satisfactory as though the serum levels had been obtained at the time of the mental testing, it is known that the serum level remains relatively constant between the fourth and the eighth day under this thera-

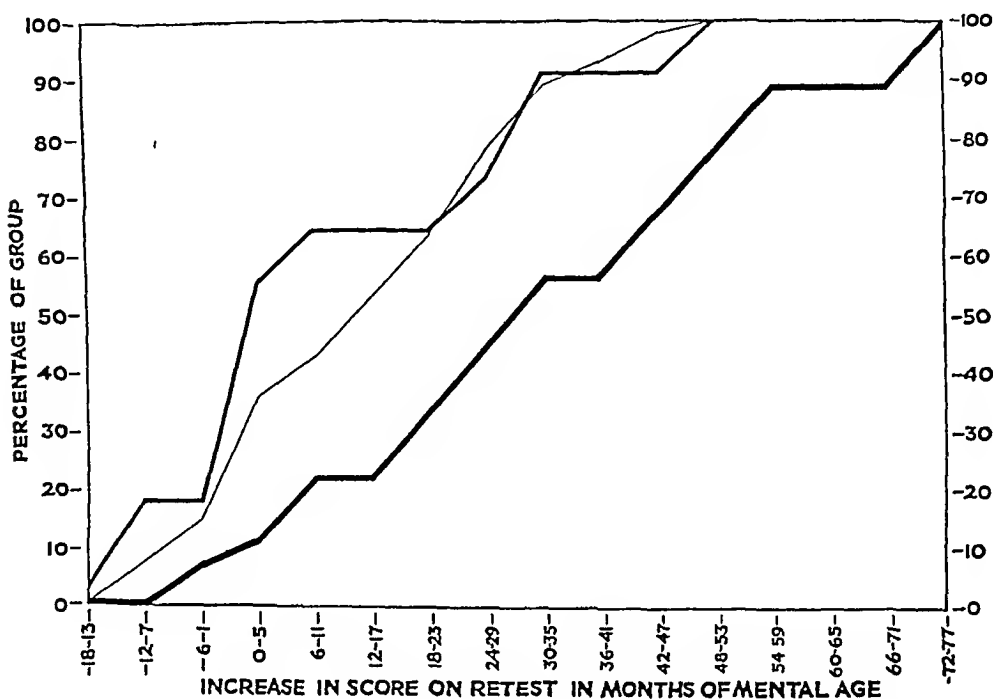


Chart 4—Cumulative frequency graphs comparing curves for the mental age scores for two subgroups of group 3 (patients given 4.5 Gm of quinacrine hydrochloride) having serum quinacrine levels above (heavy line) and below (medium line) 18 micrograms per hundred cubic centimeters, respectively, and a normal curve (light line) constructed by combining the scores for groups 1 and 2.

peutic regimen. The serum levels varied from 9 to 30 micrograms per hundred cubic centimeters, with a mean level of 18.2 micrograms per hundred cubic centimeters. Eleven patients had levels of less than 18 micrograms per hundred cubic centimeters (actually 15 micrograms or less), and 18 patients had levels of 18 micrograms per hundred cubic centimeters or above. The mean increment in mental age on the retest for the entire 29 patients was 25.7 months. The 11 patients with the lower levels showed a mean increase of 12.4 months, whereas the patients with the higher levels showed a mean increase of 33.9 months on the



retest The difference between the means is 21.5 months, a difference which verges on being statistically significant

Examination of chart 2 shows the difference in scatter in the two subgroups of group 3. It is seen that 6 of the 7 patients who showed an increase in mental age of 48 months or more on the retest had high serum levels, and the tendency for the subjects with high serum levels to show the greater increases in score is apparent. Chart 4 shows the cumulative frequency curve for the subjects in group 3 with serum levels of 18 micrograms per hundred cubic centimeters or more, contrasted with a curve for the subjects with the lower levels and with a curve for the controls, groups 1 and 2 combined. The curve for the subjects with the lower levels runs close to the control curve, whereas the curve for the subjects with the higher serum levels runs a widely separated course, as summarized in table 7.

TABLE 7—*Distribution of Improved Scores for Subjects with Serum Quinacrine Levels Above and for Those Below 18 Micrograms per Hundred Cubic Centimeters*

Increase in Score on Retest of	Combined Controls (Groups 1 and 2) 57 Patients, Per Cent	Serum Levels Below 18 Micrograms per 100 Ce., 11 Patients, Per Cent	Serum Levels 18 Micrograms per 100 Ce. or Above, 18 Patients, Per Cent
18 or more	49	36	88
24 or more	37	36	77
30 or more	23	27	66
36 or more	11	9	44
48 or more	2	9	33
54 or more	0	0	22

Although it is apparent that not all subjects with serum quinacrine levels of 18 micrograms per hundred cubic centimeters or higher show definite toxic effects on mentation, it is seen that the "impurity" of the curve for the entire group 3, as shown in chart 3, has been clarified to a large extent by the division of the group according to serum levels. The results of the testing of these small groups of patients indicates fairly definitely that, whereas serum quinacrine levels of 18 micrograms per hundred cubic centimeters and above are likely to result in toxic impairment of mentation that is measurable, levels of less than 18 micrograms per hundred cubic centimeters appear to be unlikely to cause impairment of any measurable proportions.

It was assumed in the experimental procedure that if toxic effects of quinacrine were found they would have cleared by the time of the retesting, seven days after the cessation of quinacrine therapy. The amount of the drug in the serum had fallen to a negligible level by this time. There is some evidence, which needs further checking, that the toxic

influence of the drug does not completely disappear so rapidly. This may be due to the deposition of the quinacrine in the cells or in the spinal fluid or to injury to the cells. Ten subjects were retested a second time one month after cessation of treatment. The subjects were selected for retesting because they had not shown a mental age on the second test which was as high as had been anticipated from measuring the intelligence with a vocabulary test. The rationale for this assumption will not be discussed here, as it is extraneous to the experiment, but a discussion of the problem may be found elsewhere.<sup>3</sup> Ten control subjects from group 1 were also tested for a third time. The controls showed a mean increase in score of 9.7 months between the first and the second retest, whereas the subjects who had received 4.5 Gm of quinacrine hydrochloride showed a mean increase in mental age of 23.2 months. The difference is sufficient to indicate that the results of the experiment may have been somewhat more significant if the retesting had been carried out at a longer interval after cessation of quinacrine therapy.

The data on group 4, which consisted of the 10 patients who had received 0.3 Gm of quinacrine hydrochloride daily for nine weeks before being tested, will not be analyzed in detail, as the group is too small. However, the results afford a check on the main experiment. Serum quinacrine levels were obtained on 9 patients at the time of testing. The serum levels ranged from 6 to 11 micrograms per hundred cubic centimeters, with a mean level of 8.8 micrograms per hundred cubic centimeters. The difference between the mental ages on the test during the ninth week of treatment and the retest, five weeks later, ranged from —16 to 31 months, with a mean of 7 months. The results are compatible with those obtained for the control groups. The lesser mean difference may be due to chance but more probably is to be explained by the fact that the retesting was carried out five weeks after the original test instead of just one week later, as in the control groups, a condition which lessened the importance of the learning factor. This incomplete experiment indicates that the total dose of quinacrine is not a significant factor, for these patients had received over 17 Gm of the drug when they were first tested. It tends to substantiate the evidence that levels below 15 micrograms per hundred cubic centimeters do not cause measurable impairment of mental functioning.

#### COMMENT

The experiment which is reported was originally planned as a preliminary procedure to test the method as well as the impression gained clinically that some patients who were being treated with massive amounts of quinacrine exhibited impairment of mental functioning. The fortunes of war interrupted further experiments in which the slight diffi-

culties in methodology were corrected and precluded the possibility that we should be able to carry the investigations to a more definitive termination. The results of the preliminary investigation appear sufficiently decisive to indicate that the technic is satisfactory and to provide additional knowledge of the toxicity of quinacrine for human beings.

The technic appears satisfactory, as tests on two separate control groups yielded almost identical results, whereas the scores for the experimental group, in which there was reason to believe, *a priori*, that the efficiency of mental functioning declined, indicated that some patients suffered such impairment.

A comparison of the data assembled indicates that the conventional quinacrine dose of 21 Gm given in seven days does not exert a toxic effect on mental functioning but that 45 Gm given in six days is likely to cause impairment which occasionally is rather pronounced. Further analysis of the data suggests strongly that there is a relationship between the serum quinacrine level and the deterioration of intellectual functioning. Tests on the group of subjects with serum quinacrine levels of 18 micrograms (0.018 mg) or more per hundred cubic centimeters yielded results which were definitely abnormal, whereas all groups of subjects with lower serum levels gave results which closely approximated those for the control group which received no quinacrine.

The study was motivated by the desire to clarify the problem of the quinacrine psychoses. The bulk of the psychoses which were observed on this island occurred during or after the administration of quinacrine in a dosage which was much heavier than that employed in conventional therapy. It is seen that a dosage which is sufficient to produce high serum quinacrine levels causes impairment of thinking which is at times considerable. As toxic psychoses are accompanied with, and perhaps caused by, mental confusion, it is to be anticipated that amounts of quinacrine which cause pronounced intellectual impairment will occasionally produce confusion sufficient to cause behavioral abnormalities. However, cases in which quinacrine psychoses followed conventional therapy have been reported and have been seen on this island, though extremely rarely. The etiologic factor in these cases has not been elucidated. It is possible that the patients have an idiosyncrasy to the drug and become confused even when the serum level is low. However, it is known that a rare subject will have a serum level in the neighborhood of 18 micrograms per hundred cubic centimeters after the administration of 0.3 Gm of quinacrine hydrochloride for six or seven days. It is possible that it is these subjects, who vary from the normal in rates of absorption and excretion, who may become psychotic on treatment with a conventional dose. This matter, which is of interest to the problem of idiosyncrasy to drugs in general, cannot be decided until serum levels can be determined for such patients.

The experimental results confirm the clinical impressions concerning the toxicity of quinacrine. Although quinacrine is toxic to the central nervous system, there is a wide margin of safety, and it is unlikely to exert any toxic effect whatever on the mental processes when given in conventional doses. If the experiences on this island are confirmed elsewhere, the risk entailed in producing very high serum levels is unnecessary, for the efficacy of quinacrine is not increased by such a method of treatment.

#### SUMMARY

A method of detecting and measuring the toxic influence of drugs on mental activity by means of the Kohs block test is presented, and the rationale of the procedure is discussed. The technic was applied to the study of the toxicity of quinacrine (atabrine) because the most significant toxic effect of the drug, as seen in the treatment of many thousands of patients for malaria, was the occurrence of toxic psychoses. A preliminary experiment was carried out in the determination of the dose of quinacrine which is toxic to the central nervous system. The results indicate that quinacrine given in a conventional dosage of approximately 2.1 Gm in seven days causes no toxic effect, but when 4.5 Gm is given in six days a number of subjects show impairment of mental functioning. Correlation of the results of the mental testing with serum quinacrine levels indicates that serum levels above 18 micrograms (0.018 mg) per hundred cubic centimeters tend to be toxic, whereas subjects with lower serum levels showed no deviation in intellectual functioning from that of normal controls who had received no quinacrine. The toxic levels are rarely found in patients treated conservatively. The experimental results are in accord with the clinical observations that toxic psychoses rarely occur except when massive quinacrine dosage is employed and that, while a fair number of patients receiving massive doses complain of feeling confused or intoxicated, patients under conservative treatment rarely present such complaints.

The results of the study of quinacrine toxicity suggest that the method evolved offers a new means of studying the effect of drugs on mental activity and of defining the optimal dosage when the effect on cerebration is important.

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## RING SCOTOMA AND TUBULAR FIELDS

Their Significance in Cases of Head Injury

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IN EVALUATING a patient's complaints, one is always confronted with the question whether the symptoms are "organic" or "psychogenic." If there is a history which is typical of a well defined syndrome or if a lesion can be demonstrated, the symptoms are accepted as organic. However, if the patient manifests signs of increased emotional tension or if the symptoms and signs are "atypical" or inconsistent or do not follow well known organic patterns they are often considered psychogenic. Sometimes there is a combination of the two types.

In either instance the symptoms are due to a disorder in function. The patient's reactions in the case of an organic disorder are just as functional as in the case of a neurosis. The difference between the two lies in the origin of the functional disorder and in the manner in which the symptoms manifest themselves. Nevertheless, close analysis will reveal that in many instances apparent hysterical reactions follow consistent and specific physiologic patterns, and in such cases it may be difficult to differentiate the organic from the psychogenic syndrome.

In the course of an investigation of perceptual changes in a large group of patients with battle injuries of the brain, visual disturbances were noted in a considerable number of cases<sup>1</sup>. In 1 case a so-called ring scotoma, combined with an occasional tendency toward concentric contraction of the monocular and binocular fields, was discovered.

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This article has been released for publication by the Division of Publications of the Bureau of Medicine and Surgery of the United States Navy. The opinions and views set forth in this article are those of the writers and are not to be construed as reflecting the policies of the Navy Department.

1 (a) Bender, M B, and Furlow, L T. Phenomenon of Visual Extinction in Homonymous Fields and Psychologic Principles Involved, *Arch Neurol & Psychiat* **53** 29-33 (Jan) 1945. (b) Bender, M B, and Teuber, H L. Phenomena of Fluctuation, Extinction and Completion Associated with Visual Perception, *ibid* **55** 627-658 (June) 1946, (c) Nystagmoid Movements and Visual Perception. Their Interrelation in Monocular Diplopia, *ibid*, **55** 511-529 (May) 1946.

Such visual disturbances have been considered by many authorities as psychogenic, even in cases of head injury, if pathologic changes in the retina itself could not be demonstrated.<sup>2</sup> Evidently, this functional interpretation was prompted by the fact that these field defects could not be explained on a neurophysiologic basis. But, for the same reason, this class of changes, comprising contracted fields, shifting fields, fields with spiral contour and ring scotomas, has become a domain of unlimited debate in the literature. Some of the reported observations and interpretations on this subject are reviewed in the following section.

#### PREVIOUS OBSERVATIONS

*Tubular Fields*—Concentrically contracted fields were originally interpreted as arising always from actual disease of the peripheral organ. Von Graefe,<sup>3</sup> in 1865, conceived of *anaesthesia retinae*, which appeared on perimetric examination as absolute blindness in the periphery of the field. Although he recognized hysteria as the principal causative factor, he insisted on localization of the "disease" to peripheral zones of the retina, mainly because he was able to produce pressure phosphenes in the presumably blind regions of the field. Since these phosphenes arise directly in the optic nerve, he concluded that the anesthesia must be in the retina.

It was soon pointed out that hysterical fields were often characterized by inconsistency from one examination to another and by sudden, and yet frequently transitory, improvements. Moreover, patients with concentrically contracted fields were, nevertheless, in most instances well

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2 On theoretic grounds, there is an obvious reason for grouping ring scotomas with other unusual field defects, such as shifting and spiral fields and concentrically contracted, or "tubular," fields, and for declaring all these changes to be psychogenic. The common denominator of all these fields is found in the fact that none of them can be interpreted in terms of accepted ideas of cortical representation of visual function. The usual field defects produced by focal injury to the brain correspond closely in shape, extent and location to the shape, extent and location of the injury to the optic pathway or radiation. Ring scotomas and contracted fields, on the other hand, obviously are not produced by ring-shaped or concentric lesions in the visual substrate. If their "organic" causation could be accepted in certain cases, they would seem to negate the wealth of evidence which has been accumulated, particularly since World War I, in favor of a topologic representation of the retina on a "cortical retina" (Kluver, H. *Visual Disturbances After Cerebral Lesions*, Psychol. Bull. **24** 316-358 [June] 1927). However, there are serious doubts whether the evidence for topologic representation should necessarily be interpreted as point for point correspondence in a functional sense. More recently, departures from point for point correspondence, even in cases of clear-cut "organic" hemianopsias and quadrantanopsias, have been demonstrated.<sup>1b</sup>

3 von Graefe, A. *Vortage aus der v. Graefeschen Klinik, zusammengestellt und mitgeteilt von Dr. Engelhardt*, Klin. Monatsbl. f. Augenh., 1865, p. 265.

oriented in space and quite adequately avoided obstacles and moving objects in their peripheral fields. Their contracted fields seemed to exist primarily during perimetric measurement. Wilbrand and Saenger<sup>4</sup> therefore assumed that the constriction was produced by a temporary central depression of visual activity, viz., a corticofugal inhibitory influence on the processes of assimilation in the periphery of the retina. To indicate the fleeting character of many of these disturbances, they introduced the term "central fatigue." Von Bechterew,<sup>5</sup> however, again (in 1894) made the assumption that there was hypesthesia of the retina, produced by local anemia of its peripheral zones.

In the same year, Janet<sup>6</sup> formulated the strictest "functional," and hence central, interpretation of these phenomena. For him, tubular fields were the hysterical symptom *par excellence*. They inform the examiner of the patient's basic weakness of self perception, which, in turn, leads to an inability to relate impressions to the perceiving self. While this theory might be given a truly physiologic meaning, it was widely interpreted as though some form of weakened attention were responsible for the contraction of the fields of vision. In order to disprove such theories of attention Klien,<sup>7</sup> in 1907, compared the perimetric fields obtained from frankly psychotic patients, deteriorated epileptic patients and delirious alcoholic persons, on the one hand, with tubular fields of hysteria on the other. The outlines of the fields of the psychotic subjects—presumably influenced by fleeting attention—were found to be characteristically "jagged," while the fields of hysterical patients always showed a smooth, concentric contraction. Klien's own attempt to explain such tubular fields was virtually in terms of simulation; he stated, in effect, that the hysterical person is imbued with the general idea, "I am ill", during perimetric examination this preoccupation manifests itself as "I can't see."

After the gamut of theories of causation, ranging from peripheral to central, and from metabolic disturbance to simulation, had been exhausted, World War I brought cases which to Goldstein<sup>8</sup> seemed to show without doubt that tubular fields could be the direct result of

4 Wilbrand, H., and Saenger, A. Ueber Sehstörungen bei funktionellen Nervenleiden, Leipzig, F. C. W. Vogel, 1892.

5 von Bechterew, W. Ueber die Wechselbeziehung zwischen der gewöhnlichen und sensorischen Anästhesie, *Neurol. Centralbl.* **13** 252-297, 1894.

6 Janet, P. *État mental des hystériques*, Paris, Rueff & Cie, 1894.

7 Klien, H. Ueber die psychisch bedingten Einengungen des Gesichtsfeldes, *Arch. f. Psychiat.* **42** 359-450, 1907.

8 (a) Goldstein, K. Die Lokalisation in der Grosshirnrinde, in Bethe, A., von Bergmann, G., Emden, G., and Ellinger, A. *Handbuch der normalen und pathologischen Physiologie*, Berlin, Julius Springer, 1927, vol. 10, p. 600, (b) Constriction of Visual Fields, *Arch. Neurol. & Psychiat.* **50** 486-487 (Oct.) 1943.

well defined lesions (gunshot wounds) of the brain, particularly the occipital lobes. He also made an observation of considerable practical importance. Concentric contraction of truly "organic" origin may be found with the tangent screen but not on perimetric examination. The physiologic basis of these phenomena was tentatively described by Goldstein as an abnormal fatigability of the central visual substrate. According to him, the reduced excitability of the visual substrate is generalized, involving the entire occipital cortex, and even other parts of the brain. He stressed that the concentric contraction is not due to a topologically corresponding lesion. Because of the normal physiologic inferiority of the more peripheral parts of the field of vision, he stated that the periphery is hardest hit during a general depression of visual function, thus yielding a tubular field.

*Shifting and Spiral Fields*—In plotting tubular fields, Forster discovered (according to König<sup>9</sup>) that the field was always smaller when the centrifugal motion of the target along any meridian was reversed and the target moved across the center and back toward the periphery. This shifting of the boundaries of the visual field (Forster's shift type) was considered as a means of differentiating "genuine traumatic neurosis" from malingering. It was attributed sometimes to retinal, sometimes to central, fatigue. However, it soon became evident that a similar shifting could be obtained with this form of perimetry for normal fields, although the extent of the difference between the boundaries obtained on centripetal and on centrifugal motion of the target was much less pronounced than with pathologic fields. The shifting itself seemed clearly related to the difference in threshold values found in any experimentation on psychophysical thresholds. Thus, there is always a discrepancy between measurements taken with an ascending series of intensities, which somewhere cross the visual threshold, and results obtained from a descending series, which starts above the threshold and is gradually made to fall below it. However, the exaggerated shifting in pathologic fields seemed to require an explanation. In the literature, this was attempted on the basis of two factors: inattention (fluctuation of the attention<sup>9</sup>) and retinal fatigue.<sup>4</sup> Inattention can be excluded on the basis of Klien's results.<sup>7</sup> For shifting fields the theory of fatigue seems comparatively more appropriate because in many cases it may be found that the effects which lead to the "shifting" in the field of vision become cumulative—a characteristic of physiologic fatigue. That is, every time the target is reversed and directed toward the periphery on the opposite side, it disappears there

<sup>9</sup> König, O. Ein objectives Krankheitszeichen der traumatischen Neurose, Berl klin Wchnschr, 28 774-778 1891



sooner, or at a point which is a few degrees closer to the center. If meridian after meridian is thus tested, the contraction will appear to increase continually, and the total outline of the field will present the picture of an "exhaustion curve" (Wilbrand and Saenger), frequently a spiral.

*Ring Scotomas*—It was Goldstein<sup>10</sup> who first pointed out that the obscure phenomenon of ring scotoma may be closely related to that of oscillating (shifting) fields and to concentrically contracted fields, as found in patients with organic disease. With the collaboration of the psychologist Gelb, he analyzed 6 cases of ring scotoma in battle casualties of World War I. In contrast to all previous investigators, who attributed ring scotomas either to hysteria or to specific lesions of the retina, Goldstein assumed a central causation. Although he couched his explanation in terms of cortical "fatigue," it is evident from his case reports that fatigue in his sense is directly related to mode, intensity and duration of excitation in the visual organ. He observed that with slow inward motion along every meridian a target disappears after it has reached a certain zone (Goldstein found on the average a zone extending 60 to 40 degrees from the center). This he explained in terms of "fatigue." However, with continued centrifugal motion the greater excitability of the central region of the field comes into play and the target becomes visible again, thus yielding a ring scotoma. Investigation during the period between the two wars apparently did not continue along the lines suggested by the approach of Goldstein and Gelb. From the inclusive review of literature by Strauss and Savitsky on head injuries, in 1934,<sup>11</sup> it appears as though ring scotomas in cases of injury to the brain were still attributed rather dogmatically to hysteria, or to such conditions as concurrent commotio retinae.<sup>12</sup>

10 (a) Gelb, A., and Goldstein, K. Ueber Gesichtsfeldbefunde bei abnormer "Ermüdbarkeit" des Auges (sog. "Ringskotome"), *Arch f Ophth* **109** 387-403, 1922. (b) Goldstein, K. *After-Effects of Brain Injuries in War*, New York, Grune & Stratton, Inc., 1942, (c) footnote 8a.

11 Strauss, I., and Savitsky, N. *Head Injury. Neurologic and Psychiatric Aspects*, *Arch Neurol & Psychiat* **31** 893-955 (May) 1934.

12 This was done in spite of the rarity of clearcut ring scotomas, even in cases of disease processes localized to the retina and the optic nerve. Thus, Nicoletti (Sul comportamento e significato clinico della scotoma anulare nelle affezioni delle membrane interne dell'occhio e del nervo ottico, *Ann di ottal e clin ocul* **54** 879-924, 1926) found only 33 instances of ring scotoma among 10,000 cases of disease of the eye and classified the defect as due to retinitis pigmentosa, syphilitic chorioretinitis, myopia, injury to the eye, glaucoma and optic neuritis. Langdon (Ring Scotoma, in *Contributions to Ophthalmic Science*, Dedicated to Dr. Edward Jackson, in Honor of His Seventieth Birthday, March 30, 1926, Menasha, Wis., George Banta Publishing Company, 1926, p. 274) added

Strauss and Savitsky reported 2 cases of their own, which are of interest because the ring scotomas (unilateral in the first case and bilateral in the other) were found only on the tangent screen. Although the symptoms followed severe trauma to the head in each case, the authors were inclined to assume the existence of a "functional factor" for at least 1 of their cases. On retesting the fields of their patients two to four weeks after the original tangent screen studies had been made, they found that the unilateral scotoma in the first case "was beginning to break up into islets of absence of vision." In the second case the fields appeared greatly contracted bilaterally. "The narrowing of the fields was so marked that it overlapped the site of the annular scotomas." Evidently, on reexamination the ring scotoma had been replaced by a tubular field.

In view of the fact that the majority of the authors have regarded ring scotomas and tubular and spiral fields as psychogenic, we endeavored to investigate the nature of the complex functional disorder by subjecting our patient to a series of special examinations. In our group of patients with injuries of the brain, it was noted that the introduction of psychophysiologic procedures often made it possible to understand even seem-

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commotio retinae, migraine, disease of the nasal sinuses and solar retinitis as causative factors. Ring scotomas attributed to hysteria were reported earlier by Wolfflin (*Ueber ein seltenes Gesichtsfeldsymptom bei Hysterie*, *Arch f Augenh* **65** 309-312, 1910) and de Schweinitz (*The Relation of the Visual Fields to the Investigation of Certain Psychoses and Neuroses*, *Univ Pennsylvania M Bull* **22** 282-294 [Dec] 1910), cited by Strauss and Savitsky.<sup>11</sup> Loddon (*Sur un cas de scotome annulaire par la quinine*, *Ann d'ocul* **166** 733-742, 1929) described a case of ring scotoma following quinine poisoning, and LeBlond (*Un cas de scotome annulaire bilateral d'origine traumatique*, *Ann d'ocul* **161** 740-741, 1924) reported cases of bilateral ring scotomas following head injury. Only comparatively few case reports have been added during the last ten years. Macular burning was recently shown to be responsible for ring scotoma (Loewenstein, A, and Steel, J. *Macular Burning and Ring Scotoma*, *Glasgow M J* **135** 73-85 [March] 1941). Krinsky (*Symmetric Incomplete Annular Scotoma of Tobacco Origin Without Enlargement of Blind Spot*, *Am J Ophth* **17** 722-725 [Aug] 1934) reported a case of ring scotoma associated with tobacco amblyopia. Other cases were recorded by Borsello (*Ring Scotoma in Disturbances of Optic Nerve Due to Arachnoiditis*, *Rassegna ital d'ottal* **9** 101-137 [Jan-Feb] 1940), in which the scotoma resulted from arachnoiditis, by Meyerbach and Loewenberg (*Bilateral Ring Scotoma of Five Years' Duration*, *Arch Ophth* **22**:674-678 [Oct] 1939) (in which the cause was undetermined), and by Callahan (*Annular Scotoma*, *Am J Ophth* **24** 196-199 [Feb] 1945). Lillie and Adson (*Unilateral Central and Annular Scotoma Produced by Callus from Fracture Extending into Optic Canal. Two Cases*, *Arch Ophth* **12**:500-508 [Oct] 1934, *Tr Sect Ophth, A M A*, 1934, pp 90-99) described 2 cases of unilateral central and annular scotoma due to callus from fracture extending into the optic canal.

ingly bizarre complaints<sup>13</sup> The pathologic modifications in visual function were therefore studied by a combination of available clinical methods and technics of the psychologic laboratory Perimetry and tangent screen tests were thus supplemented with tachistoscopic examinations and with studies of after-imagery, perception of movement, color, depth and apparent size Various tests of relative and absolute localization in visual space were made Thresholds for fusion of flicker were computed for different degrees of eccentricity from the macula In addition, the patient's reports were recorded verbatim and drawings obtained whenever possible (this qualitative material could be used rather safely in cases in which the damage to the brain was limited and in which the possibility of simulation and of gross forms of hysteria had been excluded) In the case reported here this triad of neurologic, psychophysiologic and "phenomenologic" methods was applied throughout

#### REPORT OF A CASE

A water tender third class, aged 28, sustained multiple injuries from shrapnel and concussion, on Oct 25, 1944, while he was engaged in fighting fires within a closed compartment of his ship He was stunned but presumably not unconscious There was immediately a deafening ringing in his right ear, but he did not notice any phosphenes or other visual disturbances Although his left hand seemed to him "stiff" and unmanageable, he was able to use all extremities in going over the side of his own vessel and in climbing over a cargo net aboard another ship which was standing by There it was found that he had wounds in his right arm, his right thigh and leg and the lower part of his left leg The left ear drum was red and torn, and the ear was draining This discharge stopped spontaneously twelve days after the injury Above the ear, in the right temporal region, there was a scalp wound, which (two months later) proved to be a compound fracture of the skull, close to the midpoint of the temporoparietal suture

For the first two months after the injury treatment was concentrated on the patient's leg wounds, which ran an irregular septic course Repeated surgical intervention was necessary for the removal of foreign bodies from the right thigh The existence of an intracranial injury was established, when the patient's complaints of severe temporo-frontal headaches and difficulties (pain) in closing his jaw persisted, even after the small wound in the scalp above the right ear had healed Roentgenographic studies on Dec 18, 1944 showed evidence of depression of the fracture near the temporoparietal suture and some indriven fragments of bone, but no foreign body A radiolucent shadow anterior to the coronal suture in the right lateral view suggested originally (on December 18) an

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13 Psychophysiologic methods require such strict internal consistency of the patient's reports that simulation or crude forms of hysteria could soon be recognized as such Nevertheless, patients with presumably psychogenic complications were not simply dropped from the series but were studied in exactly the same fashion as those with "purely organic" conditions This was done in the hope of determining the extent of similarity or dissimilarity which may exist between the visual disturbances in the so-called post-traumatic neuroses and those visual difficulties which result directly from cerebral trauma

additional fracture of the skull just above the right orbit. However, on repeated roentgenographic examinations (up to Sept 19, 1945) the latter area of diminished density could not be definitely identified (fig 1)

On Jan 4, 1945 a decompression of the skull fracture was performed. Since the patient continued to complain of pain in the head and the right side of the face, even after the decompression, further studies to determine the cause of the pain were made. Roentgenograms of the maxilla, zygoma and paranasal sinuses revealed no abnormalities. There was no clinical evidence of sinusitis.

Further neurosurgical intervention was not indicated, since neurologic examination on January 30 showed an essentially normal status except for homonymous defects in the visual fields on the left, defective hearing in the right ear<sup>14</sup> and diminished pain sensation over the left side of the body. The last defect, however, could be demonstrated only on application of simultaneous double stimulation to



Fig 1—Roentgenogram of the skull, revealing an old defect in the right temporoparietal region

corresponding parts of the right and the left half of the body<sup>15</sup>. The facial pain was finally considered to be due to a disorder in the function of the temporo-mandibular joint.

This pain, together with recurrent headaches, some dimming of vision and pronounced loss of hearing in the right ear, continued to be the patient's outstanding complaints. These symptoms were unchanged when he was seen again, one month after his discharge from the service.

#### PSYCHOMETRIC AND PERSONALITY STUDIES

Special psychometric and personality studies were made on Feb 5, 1945 by Lieut. (jg) J W Diamond. She reported the following results. On the

<sup>14</sup> On the audiogram, the hearing loss in the right ear amounted to 20 to 30 decibels for the lower frequencies, with a drop to 50 decibels in the highest range of frequencies. The fundi were normal, and the patient showed no signs of myopia.

<sup>15</sup> Bender, M B. Extinction and Precipitation of Cutaneous Sensations, *Arch Neurol & Psychiat* 54 1-9 (July) 1945.

Wechsler-Bellevue adult intelligence scale the verbal intelligence quotient was 111, the performance intelligence quotient 98 and the full scale intelligence quotient 105. The intellectual level was average. No difficulty in calculation existed. Memory for repeating digits forward was found to be superior (eight digits), but when the patient was asked to reverse the order he was unable to go beyond a series of four. With performance items, the patient did not do as well as on the verbal scale, but his ability in reproducing block designs and in assembling objects was on his average level. The Benton visual retention test<sup>16</sup> revealed no deficiency (the patient reproduced correctly 7 designs out of a total of 7). The Shipley-Hartford scale gave him a superior vocabulary but only dull normal thinking ability, "with a conceptual quotient indicative of intellectual impairment." On the Hunt-Minnesota test for organic damage to the brain, the discrepancy between expected score and actual score in learning paired words and paired designs was "extreme, and suggestive of diffuse organic disease of the brain (T score 82)." The Rorschach record, finally, was considered to be within normal limits, with none of the signs which are presumably pathognomonic of severe organic (post-traumatic) change. The only deviant trend was a tendency to pick out unusually minute details for interpretation, which, it was felt, reflected "an obsessiveness or meticulousness of personality."

Six months later, when he was retested with some of the tests which had yielded results outside of "normal" limits on the first trial, it was found that there was no longer any discrepancy between the expected score and the obtained score in the Hunt test. Retesting with specific subtests of the Wechsler-Bellevue scale indicated that all intellectual abilities were now on a fairly even average level, without any significant disparities. The psychologist noted, however, that the patient, though cooperative, was rather tense throughout the testing procedure. "He manifested a rigid, inflexible approach to the various tasks set before him and became upset with any feeling of pressure or with any hint of failure. It was noted that he either performed very efficiently or became totally lost and unable to function at all. For instance, he would learn the paired words well, then make one error and become completely confused. His general attitude was uncompromising and perfectionistic, and he showed unusual extremes in efficiency, which depended not on the type of the mental tasks but, apparently, on the feeling of pressure or impending failure." These psychologic reports are of interest, even though their evidence for an original mild post-traumatic change in personality may not be conclusive. They characterize in a clinical fashion the patient's personal "style" of functioning, which he exhibited throughout the numerous subsequent tests of his visual perceptions.

#### AWARENESS OF VISUAL DEFECT

The patient's spontaneous complaints about his vision were considerably less frequent than those about his infected leg wound, his hearing difficulties and his persistent headaches. All that he would say was that his vision was "dimmed" and that his eyes were readily tired and "watered" more than usual. When asked to specify his descriptions, he made the following statements: 1. Ever since his injury both eyes had seemed to be covered with a film or haze. This film was transparent and of seemingly equal density for the two eyes. If he closed either eye, the film appeared thicker (less transparent). It always seemed to cover

<sup>16</sup> Benton, A. L. A Visual Retention Test for Clinical Use, *Arch Neurol & Psychiat* 54:212-216 (Sept) 1945.

the whole eye evenly 2 About six months after the injury he began to be less aware of this film, noticing it only after straining his eyes, as in reading Then the blurring of images would bring the film back to his attention 3 He also noted at this time that the film seemed to fluctuate in density With prolonged fixation on any one object, it became thicker and momentarily obscured either part or all of the objects within his field of vision He would then close his eyes and wait for a few seconds, and after this his vision seemed to have recovered, until the cycle started anew 4 Whenever he closed his eyes under these conditions, the film was not immediately abolished but appeared broken up into brightly luminous dots—"a film of snowflakes" These crystal-like phosphenes covered the whole field evenly As time went on, the patient noticed these phenomena less and less, and in September 1945 they had almost disappeared 5 In addition to these diffuse changes in vision, the patient became aware, shortly after his injury, of a definite "blank spot" localized to the left corner of the left eye This spot impressed him neither as darkness nor as a film or haze, "things simply weren't there" By June 1945, or eight months after the injury, this feeling also had been "eliminated" as the patient put it 6 Even a year after the injury the patient found it impossible to drive a car unassisted As his main difficulty in this respect, he described a peculiar "jumping" of the roadside at his left, particularly on driving through a curve "The side of the road suddenly jumps out [from the left] into the middle of the road—as if I were driving suddenly beside the road, instead of driving on it"<sup>17</sup> 7 He also complained of rapid ocular fatigue, noted when he was trying to read more than a few paragraphs or when he was watching a movie for more than a few minutes "Things dim out still and then come back again"

In order to evaluate the patient's complaints, numerous clinical and psychophysiologic tests were made over a period of eight months (January to October 1945) All these tests were administered under standard conditions, that is, in exactly the same way as for other patients in our series with head injury, as well as for a group of normal subjects

#### PERIMETRIC EXAMINATIONS

Perimetric studies with an illumination of 1 foot candle, a distance of 33 cm and 1 degree targets (white and red) revealed consistently on different dates (Feb 12 to Aug 13, 1945) an absolute scotoma (semicrescent) in the periphery of the left lower temporal quadrant, reaching to within 60 degrees of the point of fixation (fig 2) The density and extent of the scotoma remained unchanged from one examination to another Significant contractions of the fields for red were not elicited at any time

#### TANGENT SCREEN STUDIES

While the results of routine perimetric examinations were consistent and remarkably unchanged from one examination to another, the use of the Bjerrum

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<sup>17</sup> The patient's description of these sudden displacements in visual space closely resembles a phenomenon which is obtained by normal subjects on observing the rapid passing of a visual stimulus (light or illuminated slit) through the aperture in a screen Under these conditions, the stimulus object "jumps" into the field, i e, it is already considerably past the edge of the diaphragm when it is first perceived (Frohlich phenomenon [Frohlich, F W Die Empfindungszeit, Jena, Gustav Fischer, 1929, p 365])

screen led to a seemingly confusing array of results. The readings changed as time went on, but they also differed on any single day with different methods of examination.

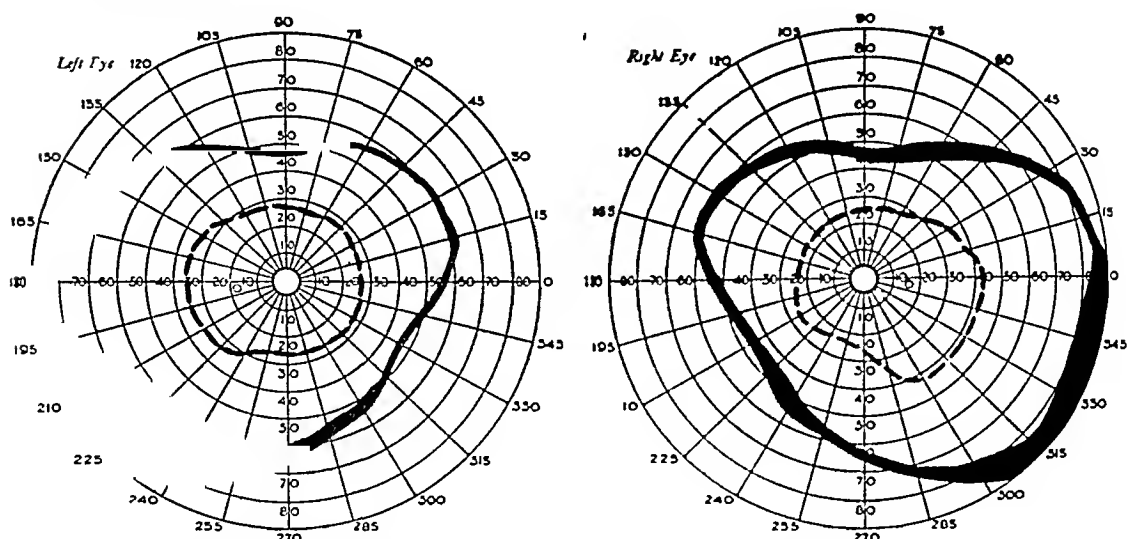


Fig 2—Perimetric charts, illustrating crescent defect in the left lower temporal field of vision. Solid black indicates an absolute scotoma for no 1 degree target at a distance of 33 cm and with 7 foot candle illumination. Lines of dashes represent boundaries of the color field for red plotted under the same conditions.

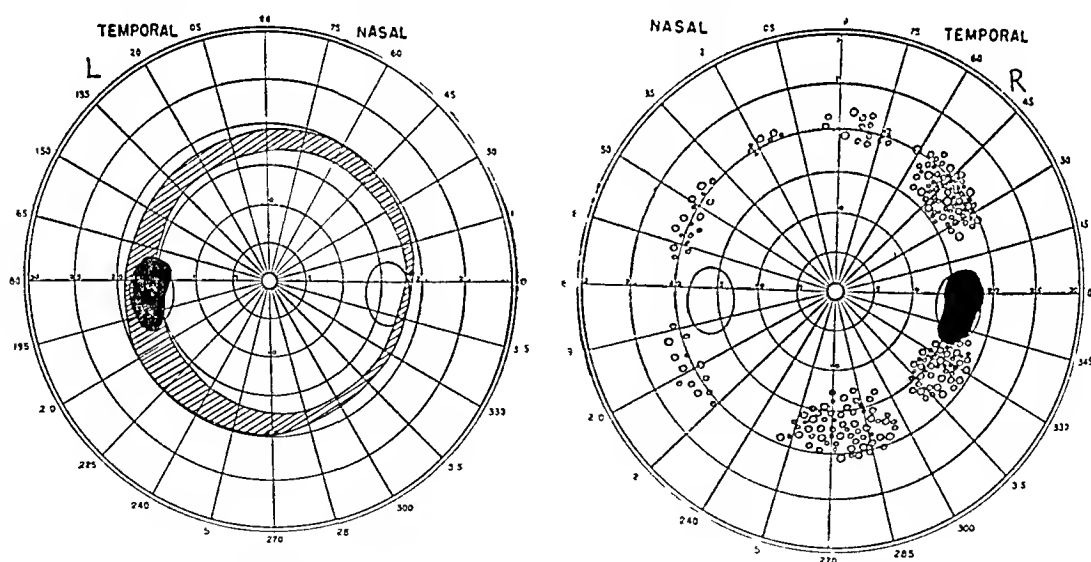


Fig 3—Tangent screen field charts, illustrating a relative ring scotoma in the left eye and an incomplete ring scotoma in the right eye. Solid black represents the physiologic blindspot. Diagonal lines in the left eye indicate the region in which a 2 mm target at a distance of 1 meter disappeared. Small circles in the right eye designate islets of impaired vision. See text for details. Note that the annular scotoma is more pronounced in the eye opposite the cerebral lesion.

On Feb 13 and Feb 20, 1945, central fields were taken on a Bjerrum screen with a 2 mm target. The patient was seated 1 meter from the fixation point. The targets were brought in (from 30 degrees to the fixation point) with slow, steady,

centripetal motion along each half-meridian. When the left eye was tested under these conditions, the target disappeared within an annular zone in the field of vision (fig 3). This zone occupied a region between 15 and 20 degrees of the fixation point. The heaviest portion was always found on the temporal side of each eye. If a larger target was used or if the patient's distance from the screen decreased, the "ring" sometimes became incomplete on the nasal side. Likewise, a different field resulted with rapid centripetal motion of the target, under these conditions the "ring" was found as much as 5 degrees closer to the center, or it was not found at all. With centrifugal motion of the target, the "ring" was usually not encountered until the target had been moved beyond 20 to 25 degrees from the center. Actually, then, the zone of disappearance no

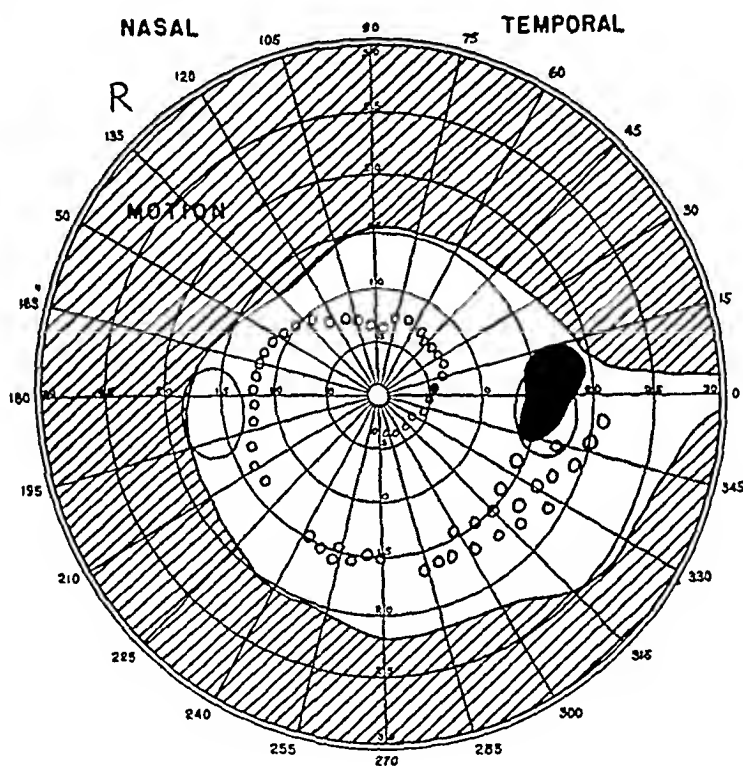


Fig 4—Chart of the central field of the right eye, plotted on the tangent screen. A 2 mm target at a distance of 1 meter was moved slowly inward from the periphery toward the fixation point. The test was started at the zero (right horizontal) meridian and repeated for each meridian in a clockwise succession. This yielded a contracted, or tubular, field for form and color but not for motion. The boundary of the field is defined by the diagonal lines. The small circles represent zones of impaired vision. Note the spiral shape. The field for the left eye was similar to that for the right eye except that it was more contracted.

longer represented an annular scotoma. In most instances the target did not reappear with continued outward motion once it had become invisible, between 25 to 30 degrees from the center. The apparent ring scotoma had thus changed into a tubular field.

When the right eye was tested with the same series of varied conditions, corresponding results were obtained. However, a definite (continuous) ring zone of amaurosis was never established. Instead, numerous small "islands" of relative loss of vision were found between 15 and 25 degrees from the fixation point. In these areas the target was indistinct and colorless, fluctuated in visibility or



became entirely extinct (fig 3) In comparing the fields of the two eyes, it was apparent that the annular defect was more complete in the field contralateral to the lesion A similar difference between the two eyes had already been noted on perimetric examination

With further tangent screen studies, it was found that when the direction of the moving target was reversed (outward) a transition into a kind of tubular field appeared in the right eye, just as it had been noted for the left eye A particularly unusual picture (a type of spiral field) resulted whenever the 2 mm target was led very slowly centripetally along each half-meridian in a clockwise order, starting from the zero meridian (fig 4) Under these conditions, the targets appeared later and later during each test, or, to put it differently, the plotted field seemed to contract more and more as the examinations progressed However, the target became immediately visible anywhere within the area of apparently reduced vision if it was moved more rapidly or was repeatedly shaken In addition to this spiral contraction, a spiral zone of fluctuation and extinction was encountered Along any meridian, after the target had first become visible, there was a tendency for the target to dim or fade out once again as the centripetal motion of the test object was continued

Examinations repeated over a period of ten months yielded practically identical results, provided that the methods of testing were kept the same The only change noted was a breaking up of the apparent ring scotoma into islands of impaired vision This was found in the left eye two months after the ring scotoma was first discovered From this time on the fields obtained on examining the left eye were similar to those found in the right eye The ring scotoma in the left eye was no longer complete There was an annular zone of "islands" of impaired vision (characterized by fluctuation and transient extinction of images) in each eye

#### DEPARTURES FROM GEOMETRIC OPTICS

Examinations with the tangent screen thus gave a complex and variable picture Sometimes concentrically contracted fields, similar to the "tubular vision" of the hysterical patient, were found In view of this, special studies were made in order to check on the consistency of the patient's reports Should his responses prove to be consistent the same studies would be extended to investigate what influence these particular field changes had on his visual perceptions

First of all, the patient's distance from the tangent screen on which the field tests had been made was systematically varied Increase in distance from the screen obviously entails a proportionate increase in the linear projection of the visual angle Thus, a contracted field of genuinely organic origin should show an apparent widening with increase in distance Under the same conditions, a tubular field produced by hysteria or simulation either remains unchanged in its apparent diameter (absolute width on the screen) or varies in random fashion With our patient, increase in the distance from the screen led *pari passu* to an (apparent) widening of the diameter of the ring-shaped "scotoma" However, this widening was found on repeated measurements to fall somewhat short of that required by geometric optics Instead of subtending a constant visual angle, the ring became increasingly broad, and at the same time its diameter was somewhat shortened (relative to the visual angle) whenever the patient moved away from the screen The same relationships held for conditions under which a concentric contraction or tubular field was obtained instead of (or in addition to) the apparent ring

scotoma In relative terms, the fields were found to be shrinking, rather than remaining constant, with increase in distance However, the extent of the shrinking did not approach the tubular contraction of the hysterical subject, who claims that his field is just as small at short distances as it is at long distances

#### AUBERT-FORSTER PHENOMENON

It will be remembered that in spite of repeated examinations neither ring scotoma nor concentric contraction could be found in this patient on standard perimetric studies These field changes could be demonstrated only with the tangent screen method Earlier, Goldstein<sup>8b</sup> had pointed out that contracted fields of "organic" origin were often characterized by just this peculiar discrepancy The main difference between the tangent screen method and perimetry in the plotting of fields lies obviously in the fact that with increasing distance from a point of fixation a target on the screen is also increasing its distance from the patient's eye

There is experimental evidence<sup>18</sup> that the acuity of peripheral portions of a normal field of vision diminishes with increasing distances of the objects viewed Thus, when a test object situated 15 degrees from a point of fixation is resolved at 1 meter, it may not be resolved at a distance of 2 meters and an eccentricity of 15 degrees even though the linear dimensions of the test object have been increased in geometric proportion This effect is known in the literature as the Aubert-Forster phenomenon Like the phenomena of size constancy,<sup>19</sup> this peculiarity of the periphery of the visual system constitutes a departure from the behavior which one would expect on the basis of strict geometric optics

In our series of cases, the Aubert-Forster phenomenon was routinely studied under the following conditions The patient was first seated at a distance of 150 cm from a tangent screen While he maintained binocular fixation on the center of two concentric circles (diameters, 13 and 26 cm, respectively), his peripheral acuity was examined This was done either by means of Snellen's test types or by means of two white cards bearing one or two dark test lines Each of the test lines was 2 cm long and 2 mm wide On the card bearing two parallel test lines, the lines were 5 mm apart These cards were introduced from the periphery with moderately slow centripetal motion along each meridian In at least three successive trials the point at which the patient was able to resolve the double line was ascertained After all readings under these conditions ("large-far" constellation 150 cm distance, 2 cm test lines) had been determined, the patient was moved to a distance of 75 cm from the screen, the examinations were repeated with test cards bearing lines which were half as large ("small-near" constellation test lines 1 cm long, 1 mm thick and 2.5 mm apart) as those used at a distance of 150 cm At the 150 cm distance normal subjects usually managed to resolve the double line at about 10 degrees from the fixation point, at the 75 cm distance the same subject resolved the double line at 13 to 15 degrees

18 (a) Aubert, H *Physiologie der Netzhaut*, Breslau, E Morgenstern, 1865  
(b) Jaensch, E R *Zur Analyse der Gesichtswahrnehmungen*, *Ztschr f Psychol u Physiol d Sinnesorg* (supp) 4 1-338, 1909 (c) Freeman, E *Anomalies of Visual Acuity in Relation to Intensity of Illumination*, *Am J Psychol* 42 287-294, 1930

19 Boring, E *Sensation and Perception in the History of Experimental Psychology*, New York, D Appleton-Century Company, Inc, 1942

from the fixation points. In other words, an Aubert-Forster phenomenon (or tendency toward concentric contraction of the functional field with increase in distance) can be noted for normal subjects under the conditions specified here.

As compared with the controls, our patient showed not only a pronounced reduction in peripheral acuity under all conditions but a disproportionate value for the Aubert-Forster phenomenon. With the "large-far" constellation he resolved the double line at 4 to 7 degrees, while with the "small-near" constellation he resolved the two lines at 8 to 10 degrees, from the fixation point. The inferiority of the "large-far" constellation as compared with the "small-near" constellation was evidently considerable. The results indicated that his fields were indeed contracted, but in a highly systematic fashion. Actually, it was not only a concentric contraction in the coronal (frontal-parallel) plane, but a drop in peripheral acuity in all three dimensions, thus producing a somewhat conical, or domelike, rather than a tubular (cylindric), contraction.

#### TACHISTOSCOPIC EXAMINATION

In all cases of our series, the various studies of visual fields were supplemented with tachistoscopic examinations. The latter tended to bring out minimal defects which could not be elicited by perimetric measurements or tangent screen tests. On the other hand, the tachistoscopic method sometimes revealed retention of visual function in areas in which perimetric studies indicated amaurosis.

Tachistoscopic examination of this patient elicited normal responses when he was confronted with a standard set of slides, exposed to either one or both eyes at a speed of 0.1 second or faster. There was neither the generalized slowing in recognition, sometimes found in cases of extensive damage to the brain,<sup>8a</sup> nor any significant tendency to miss large details in any region of the field up to 25 degrees from the point of fixation. In other words, the apparent ring scotoma and other discontinuities in the field as obtained on the tangent screen were not found on rapid (0.1 second) exposure. This is not surprising in view of the fact that in some instances the patient could see more on rapid than on prolonged exposure of a test object.<sup>1b</sup>

#### PROLONGED EXPOSURE OF SIMPLE STATIONARY PATTERNS

If the patient fixated an object for more than ten seconds, he reported dimming, fluctuation in distinctness and intensity, and occasionally total extinction of the image. This was particularly apparent with simple configurations which were large enough to involve pericentral regions. For instance, the patient drew what he saw at various stages while fixing at the center of two concentric circles on a screen situated 75 cm from the eye. He reported that first the outer and then the inner circle disappeared within fifteen to twenty seconds of continued fixation. This obliteration occurred in a discontinuous and irregular fashion. It appeared as a "fragmentation" of the field of vision. This fragmentation was more evident when a peripheral target was added to the field at 25 degrees (just outside the annular zone of continual fluctuation) and the patient was instructed to focus his attention on this stationary peripheral target while maintaining fixation in the center (fig 5 C). In these circumstances, the outer circle tended to split, first closest to the peripheral target, then rapidly in many other places. Subsequently, the peripheral target itself would disappear, and in extreme cases the

inner circle, and even the center of fixation, would temporarily "black out" (see patient's drawings, fig 5  $C_1$  to  $C_3$ ) If the patient was permitted to move his eyes or to close and reopen them, the complete image reappeared, but with continued

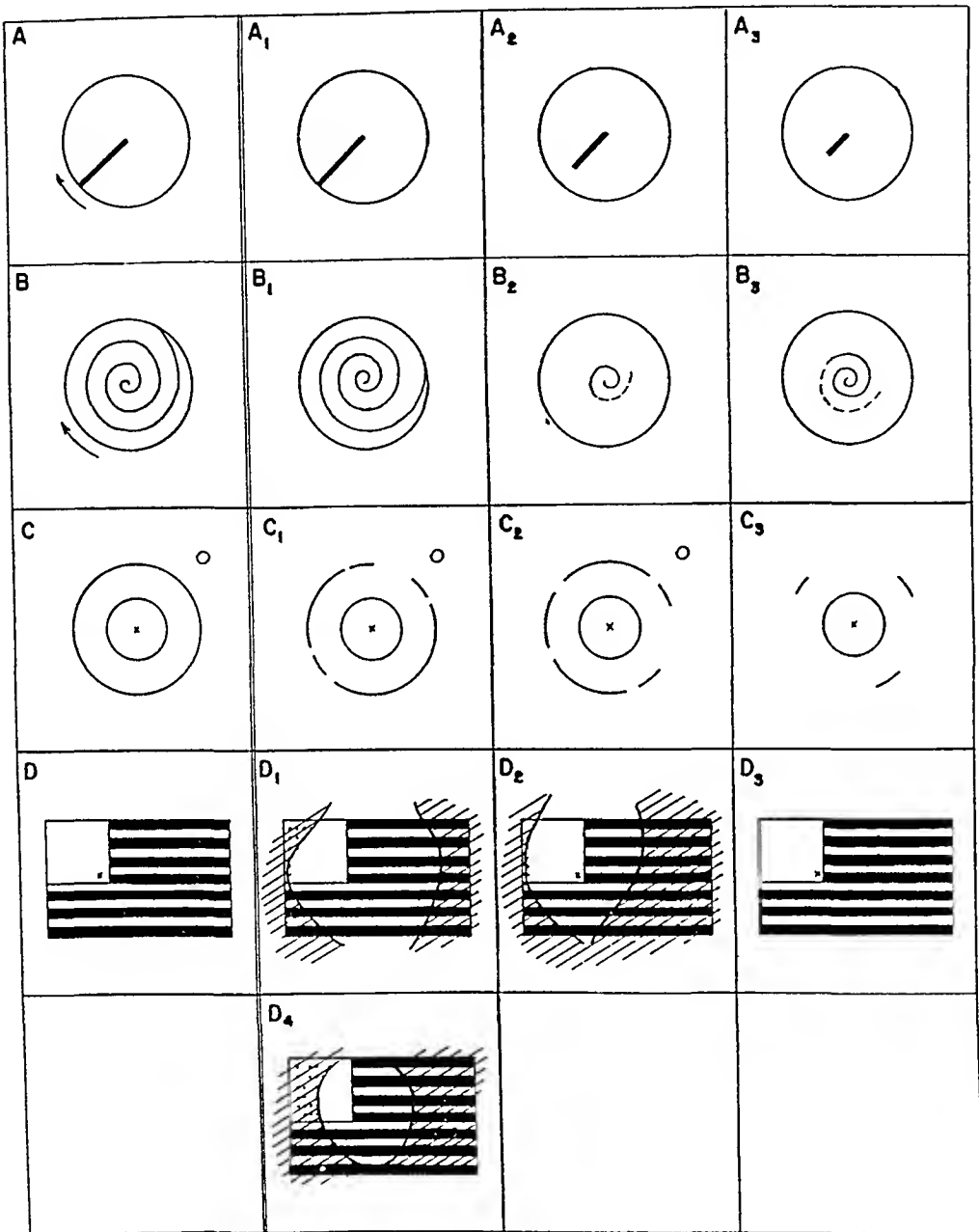


Fig 5—Various diagrams illustrating the concentric nature of the patient's visual defect (A) The patient was shown a rotating Masson disk  $A_1$ ,  $A_2$  and  $A_3$  depict what he saw as rotations continued, the black line contracted successively toward the center whenever it swept through the left lower quadrant (B) Rotating disk (plateau spiral) was shown the patient What he saw is indicated by  $B_1$ ,  $B_2$  and  $B_3$  Note the concentric shrinking of the spiral in  $B_2$ , interspersed with partial recovery ( $B_3$ ) (C) The patient was instructed to fix at X and simultaneously attend to a target (small circle in the right upper quadrant) What the patient saw is indicated in  $C_1$  to  $C_3$  Note the fragmentation and resultant contraction of the image In  $C_3$  the peripheral target (small circle) has disappeared (D) The American flag in complementary colors was used in tests of after-imagery  $D_1$  to  $D_4$  represent a succession of phases of the negative after-image Note again the gradual contraction of the after-image, interrupted by a phase in which the image was momentarily complete ( $D_3$ )

testing the periods of complete obliteration became longer and occurred more frequently. However, the recovery was always complete, at least momentarily, if the patient closed and reopened his eyes.

#### AFTER-IMAGERY

In a similar fashion, the patient's after-images tended to run through abnormally rapid cycles of disappearance and reappearance. Moreover, the patient's after-images decayed in a strangely irregular, but always concentric, fashion. He was able to obtain a strongly colored negative after-image on prolonged fixation on a drawing of the American flag printed in complementary colors (fig 5 D)<sup>20</sup>. However, the first appearance of the after-image took place only with an abnormally increased latency, regardless of whether it had developed monocularly or binocularly. Moreover, the first after-image was often incomplete, at times the patient reported a gap "1 inch wide" in the flag to the right of the point of fixation. In such an area the flag was invisible, or very faint and gray. Frequently only that portion of the flag which was to the right of the median plane was visible. When the after-image disappeared and then reappeared, only the portion to the left of the median plane was seen.<sup>21</sup> However, the most frequent course of the patient's after-images was as follows (fig 5 D<sub>1</sub> to D<sub>4</sub>). The first appearance was fully colored and more or less complete. Then the image disappeared and reappeared "with all four corners cut off." The next phase would often again be a complete image, followed by an image showing further obliteration of peripheral portions, and so forth, through ten to fourteen cycles within a minute or a minute and a half, until the after-image had faded away. In summary, visual after-imagery disclosed a concentric contraction of the field of vision, which seemed to take place as a continual process.

#### COLOR PERCEPTION

The patient's color sense, as tested with routine clinical methods (Ishihara plates, Jenning's wool skeins) appeared to be normal. However, on prolonged fixation on yellow, red or blue squares (5 by 5 cm) exposed on a milk glass screen (40 cm from the patient's eyes), the patient reported that the color faded rapidly from the edges toward the center. This decrease in chroma took place within the first twenty seconds of fixation. Sometimes, alternately the horizontal and then the vertical edges became colorless. The "fadings" were often interspersed with moments in which color was restored evenly to the whole square. If two squares of the same color were presented with time exposure (8 degrees to either side of the point of fixation), after the first few seconds, alternately the one on the left or the one on the right, or both, would become gray (i.e., colorless). After twenty to thirty seconds either one or both squares began to disappear and reappear in random fashion.

However, on tachistoscopic exposure of these colored squares, usually both squares were reported, the patient also reported positive after-images on these exposures. But either one or both of these squares tended to be colorless ("dark"), and this tendency increased with increasing speed of exposure. At a speed of

20 This test card measured 10 by 18 cm. It was placed in the frontal-parallel plane at the level of the patient's eyes, and fixation was maintained on the star in the lower right corner of the field of stars for thirty and/or sixty seconds at a distance of 30 cm.

21 These peculiarities of the patient's after-imagery were most pronounced on stimulation of the left eye. But they were also found on testing the right eye or both eyes under the same conditions.

0.01 second, when normal observers under our conditions had no difficulty in appreciating an intense single color, the patient saw only colorless (dark) squares, followed by two dark after-images, which faded almost immediately. These tests indicated a general, but slight, reduction in perception of color.

#### SPATIAL ASPECTS OF PERCEPTION

There were no gross disturbances in depth perception proper. Sizes and distances were gaged with practically normal accuracy. Evidently, the so-called perceptual constancies (constancy of size, shape and color) were not affected by the abnormality of the fields. However, objects moving in the periphery of his field frequently showed the peculiar "jumping" of which the patient had complained spontaneously. This, in a sense, could be called a disorganization of visual space, although it was most likely an expression of the abnormally pronounced fluctuation and extinction of images in the patient's periphery. (He would be aware of an incoming object for a moment, then it would become extinct and then reappear suddenly, after it had come closer to the center of the field.) Possibly, this particular difficulty was related to a disturbance in fixation which the patient showed, especially whenever he was asked to judge distances and sizes. He constantly turned his eyes and head to the left (i.e., in the direction of the principal scotoma). The occasional "jumpiness" even of stationary objects in the periphery might have been due to these ocular movements, which carried images of the objects alternately into and beyond the peripheral zone of decreased vision.

The patient's behavior in bisecting lines strongly pointed in the direction of an "organic" contraction of the field. He was instructed to attempt to bisect a line 15 cm long at a distance of 30 cm from his eye, with fixation maintained at one end. Regardless of the meridian in which the line was turned, the patient divided the line near the fixation point, making the peripheral portion too long. This occurred both with monocular and with binocular fixation. Indirectly, this was a manifestation of a concentric contraction of the field of vision, inasmuch as the peripheral portions of the lines seemed shorter to the patient than they actually were. When he was instructed to fixate the midportion of the line, he still erred considerably, but he then showed a consistent tendency to make the portion to his left too long. This was in keeping with the scotoma in his left temporal field of vision. In point of fact, a normal subject will (on monocular fixation) slightly overestimate the temporal portion of a given line if the line is oriented along the horizontal meridian. But this error in bisection of the normal subject rarely exceeds 0.3 per cent of the total length of the line.

With the stereoscope, the patient had the greatest difficulty in obtaining a Panum phenomenon.<sup>22</sup> The depth effect produced by horizontal disparity of two

<sup>22</sup> Panum (Woodworth, R. S. *Experimental Psychology*, New York, Henry Holt & Company, Inc., 1938) was the first to note that an impression of tridimensionality was obtained on exposing stereoscopically two pairs of parallel vertical lines, provided that the distance between one pair of lines was slightly in excess of the distance between the other. His observation became one of the crucial experiments for the classic theory of binocular depth perception (which assumes horizontal disparity of retinal points as the principal "clue" for depth). In the more recent work on perception of visual space (Werner, H. *Dynamics in Binocular Depth Perception*, Psychological Monographs no. 218, Columbus, Ohio, Psychological Review Company, 1937, vol. 49, no. 2, p. 1), the Panum phenomenon is considered as only a special manifestation, but still illustrative of the general dynamics of binocular depth perception.

pairs of parallel vertical lines, where each pair is presented to one eye, was never observed. If two pairs of circles were substituted for the lines, a depth effect could be obtained, although it was transient and produced intense binocular rivalry. However, binocular rivalry was not the principal difficulty in his stereoscopic vision. If three letters (*X Y Z*) were presented in such a way that each letter had to be built from monocularly presented half-images, a curious form of rivalry resulted which involved portions of the images of the letters to the right (*X*) and left (*Z*) but not the letter in the center (*Y*). The *X* as well as the *Z* appeared either distorted or incomplete, the *Y* appeared normal.

### STROBOSCOPIC MOTION

A stroboscopic effect was produced as follows. On a vertical panel, a black disk rotated at variable speed. The speed was controlled by a rheostat, and the instrument was calibrated over a range of zero to 56 rotations per second<sup>23</sup>. On the black disk two white strips of paper were fastened, the larger one being nearer the periphery and the smaller strip diametrically opposite it and closer to the center. A gray screen was placed in front of the panel. In this screen two small apertures were cut (oblongs, 2 by 1 cm, one 3 cm above the other) and placed in such manner that they would alternately expose portions of the white strips on the rotating disk. When the upper strip rotated through the upper window, the lower window was black, as the disk continued to turn, the upper window became black, and the lower window exposed the white strip. At low speed this succession was seen as such, i. e., as an alternation of black and white. With increase in speed a gray flash appeared, which seemed to move swiftly (with each half-turn of the disk) from window to window across the gray screen. At still higher speed the windows seemed to flash simultaneously, until each became a uniform dark gray. The screen was adjustable in such a manner that the apertures could be brought into any meridian of the patient's field. Furthermore, a movable fixation mark was provided, so that the windows could be observed by the patient at any desired degree of eccentricity.

In this particular case, observations could not be made at more than 10 degrees from the center because the patient was unable to resolve the two windows at greater distances from his point of fixation. The observations were complicated by a particularly rapid "dimming" and frequent temporary extinction in the tested zones of the field of vision. However, we could ascertain the following departures from the behavior of normal subjects on this test<sup>24</sup>.

(a) A lowered threshold for stroboscopic motion (appearance of the gray flash across the screen) occurred in central fixation and as far as 5 degrees from the center along each 45 degree meridian.

(b) At an eccentricity of 10 degrees along each 45 degree meridian in each quadrant, the patient did not obtain a clearcut stroboscopic effect. Instead, the impression of successive alternating flashes changed with increasing speed directly into the impression of simultaneous flicker. Under these conditions, normal observers showed a strong stroboscopic effect at such a degree of eccentricity.

23 Lieut Comdr D R Sword, U S N, United States Naval Repair Base, San Diego, Calif, designed the multiple purpose instrument which was employed in these and in numerous other studies on perception of color and motion and supervised its construction and calibration.

24 Details and quantitative data, together with the standards derived from experimentation with normal controls, will be presented separately in a report on perception of motion in defective visual fields.

(c) If a stroboscopic effect in the periphery was obtained in the patient under these conditions, it tended to be partial or fragmentary. That is, only one of the windows jumped part of the distance toward the other, which flickered but remained stationary (singular motion), or both windows were seen by him as bouncing toward each other "as if they wanted to get together, but they snap apart before they meet" (dual motion).

(d) These fragmentary stroboscopic effects were noted only on increasing the speed to 26 rotations per second for the right upper quadrant of the binocular field of vision, which represents nearly one and one-half times the speed at which optimal motion could be obtained in the center (17 rotations per second). In order to obtain motion for the right lower quadrant, the speed of the apparatus had to be increased to 35 rotations per second, or to almost twice the speed necessary for the center.

(e) In the left half of the binocular field partial motion was obtained for the upper quadrant, but only occasionally, and not until the speed of 46 rotations per second had been reached. The left lower quadrant yielded motion with a speed of 9 rotations per second, that is, only after the state of simultaneous flashing (flicker) had been reached for all other quadrants, as well as for the center. The effect was transitory, and perhaps was nothing but the usual "bobbing" of peripheral objects which had always been noted, particularly in this quadrant. These tests showed that even the more central parts of the left lower quadrant were defective.

#### FLICKER AND FUSION

It was noted throughout our series of cases of cerebral injuries that one of the strictest tests of relative field defects is the evaluation of fusion frequencies of visual flicker in various parts of the field. Particularly in resolving hemianopsias, a lowering of the threshold at which an intermittent light stimulus appears to be steady (fused) may be the last sign of a field disturbance long after perimetric examination has failed to show any pathologic condition.

For this patient, flicker was produced by means of a small Masson disk<sup>25</sup> rotated on the panel used for the series of stroboscopic observations. The thresholds for fusion under these conditions proved difficult to determine, since the images tended to fluctuate spontaneously for the patient, so that he was at a loss to indicate at which moment the "actual" flicker had stopped. (a) There was an abnormal variability of threshold even on central fixation. (b) In spite of this, the threshold for fusion was clearly lowered for the center as compared with results obtained from normal observers under our conditions.<sup>26</sup> (c) As compared with the normal, the various quadrants showed further decreases in threshold values, with the greatest dip in the left lower quadrants, again demonstrating decrease in another type of visual function of the peripheral field.

#### TRUE MOTION

The patient had some difficulty in judging the relative and absolute speeds of objects, which may have been somewhat related to his difficulty in fixation and

<sup>25</sup> A white disk with a single black line drawn from center to periphery, resembling the dial of a clock with a single hand.

<sup>26</sup> Quantitative data, together with observations on normal controls, will be presented in a separate report on flicker and fusion in defective visual fields.



pursuit (For normal observers, the phenomenal speed of a moving object tends to be higher when the object is regarded while it moves past a stationary point fixated by the subject, the speed appears to be lower if the subject follows the moving object with his gaze)

However, the most outstanding disturbances were noted in this patient when continuous motion of an object involved large portions of his field of vision. A moving stimulus was again provided by a Masson disk. This disk was rotated relatively slowly (at speeds of from 1 to 35 rotations per second) while the patient maintained fixation on the center of the disk at a distance of 35 cm under standard illumination. The patient soon became aware of a curious effect. The "hand of the clock" shrunk with each rotation, beginning at the periphery (fig 5A). This shrinking seemed to occur in a discontinuous fashion, whenever the black line swept through the left lower quadrant, it contracted a little farther. If the Masson disk was replaced with a rotating black spiral on a white ground (a stimulus used by us in the experimentation with motion after-images), the patient announced an analogous effect (fig 5B). The spiral seemed to shrink progressively as rotations continued.

#### COMMENT

At first glance, the results from this array of tests are so varied that one might be tempted to interpret the case as one of hysteria. An additional basis for such a suspicion is the persistence of the visual disturbances as such.<sup>27</sup> On the other hand there was nothing in the man's previous history or in his behavior during the period of observation to suggest a hysterical disorder. Special personality studies did not reveal significant neurotic reactions.

Moreover, there were several organic features in this man's illness, such as (a) a penetrating wound of the skull, (b) a temporal crescent defect in the field of vision in the contralateral eye and (c) consistency of his responses whenever he was subjected to the same test on various occasions. However, it was pointed out that on different tests his responses were discrepant and at times atypical. The most apparent of these seemingly contradictory observations were the following: (1) the discrepancy between the fields as determined with the perimeter and with the tangent screen, (2) fluctuations in visibility of the targets on different examinations and at different times during a single examination, (3) the apparent ring scotoma itself and its variations (notably the "breaking up" into islets of amblyopia), (4) the difference between the right and the left field of vision, (5) the frequent transitions from ring scotoma to contracted fields, and (6) the spiral contour of the field found occasionally with the tangent screen. Most of these points, in isolation, would indeed seem to suggest a psychogenic disturbance. However, interpreted in conjunction with each other, and with the patient's perceptual difficulties, the same data assume the character of an organic picture.

27 In many patients of our series with involvement of the occipital lobe, who were followed from the early stages of nearly complete amaurosis through stages of visual disorientation up to the stage of some degree of functional reorganization of the field (Bender, M. B., and Furlow, L. T. Visual Disturbances Produced by Bilateral Lesions of the Occipital Lobes with Central Scotoma, *Arch Neurol & Psychiat* 53 165-170 [March] 1945), improvement was rapid, with regard both to objective signs (field changes) and to subjective complaints. However, it was noted that our patient did improve, particularly with regard to the subjective aspects of his visual defects.

Furthermore, closer analysis of the results will show that the inconsistencies are more apparent than real. Actually, they are due to the variations in the tests themselves (as psychophysiologic situations). The patient's responses varied strictly in accordance with the differences in the stimulus situation.

1 *Discrepancies in the Visual Fields as Plotted on the Tangent Screen and the Perimeter*—First of all, the continued failure of standard perimetry to reveal ring scotomas or concentric contractions of the fields merely points to the specific role of the tangent screen in visual examinations. For simple physical reasons, only the tangent screen method will bring out a shrinking of the peripheral fields for distant objects (Aubert-Forster phenomenon). The patient's tubular fields obtained under our specified conditions might thus be understood as a variation from the norm, but from one which, in itself, embraces a wide range of varying degrees of concentric contraction.<sup>28</sup> As Goldstein<sup>8b</sup> has pointed out, even a considerable degree of contraction of this sort may be a sign of organic damage.

2 *Fluctuation in Vision*—A great deal of "fluctuation" is always encountered in testing the peripheral zones of the normal field.<sup>29</sup> This is particularly evident for such performances as the discrimination of patterns. For instance, in testing for the Aubert-Forster phenomenon in the normal subject, the subject complains of the following: "The test lines are visible for a few seconds, they disappear and reappear," or "they appear clearly as two lines for one moment and then merge again into one heavy line." Such fluctuations were manifest in our patient not only in the periphery but in the field as a whole. However, the fluctuation was most pronounced at the periphery and decreased as one approached the center except for the ring zone, in which (originally for the left eye, at least) images became completely obliterated.

3 *Ring Scotoma*—This ring zone of defective vision in the left eye, as well as the annular region, studded with islets of apparent blindness, in the right eye, were not scotomas in the true sense of the word. It is submitted that ring scotoma as an after-effect of cerebral injury is always a misnomer. For both the distance of the ring zone from the center, as well as its density, its width and even its completeness, varied with different methods of examination. These variations were systematic, i. e., a certain specified method would always decrease, and another method would increase, the apparent field disturbance. Among the factors which increased the amblyopia was primarily the slow continual motion of the target. This (next to prolonged exposure of stationary patterns) led inevitably to obliteration or "extinction" of the image. The obliteration, how-

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28 To be sure, the universality of the Aubert-Forster phenomenon in normal observers has more recently been questioned. Freeman<sup>18c</sup> has shown that the inferiority of the periphery in the "large-far constellation" fails to appear when the test objects are kept in one place and only the distance of the test lines from each other is gradually increased. But it appears all the more important that even in Freeman's control experiments the discrimination of distant stationary patterns in the periphery seems to be more difficult than the discrimination of closer patterns of identical retinal size.

29 In the normal visual field, fluctuation in intensity and distinctness, fading of color and similar phenomena are characteristic not only of the periphery but also of the region surrounding the normal blindspot (Foucault, M. *Les sensations visuelles élémentaires en dehors de la région centrale de la rétine*, *Ann psychol* 22 1-20, 1920).

ever, was not immediate. The target could be moved centripetally for a brief interval, at the end of which obliteration occurred. Thereby the semblance of a ring scotoma was produced. Moreover, the obliteration was transient, i.e., it actually was only a fluctuation. This explains the appearance of islets of amblyopia or apparent amaurosis. As the slow centripetal motion of the target continued, it invariably became visible again. This was possible because of the physiologic superiority of the central region of the field.

4 *Difference Between Right and Left Field of Vision*—It will be noted that the apparent ring scotoma in the left eye was more complete than that in the right eye. Furthermore, when, on subsequent examinations, the ring scotoma in the left eye had been replaced by annular zones of islets of impaired vision, the disturbance was again greater than the corresponding, and similar, defects in the right eye. The discrepancy in fields was also observed on perimetric examination. The half-crescent scotoma was found in the periphery of the lower temporal quadrant of the left field of vision, a homonymous scotoma in the right field of vision could not be uncovered. Since the wound of the skull was on the right side, it is presumed that the visual pathways on the right side were injured. This produced the temporal crescent defect in the contralateral eye. In a previous communication,<sup>1b</sup> it was pointed out that objective and subjective visual disturbances were more pronounced in the eye opposite the side of the cerebral lesion. This occurred even in cases in which the plotted scotomas were homonymous and congruent. Inasmuch as our patient had a focal lesion in the right hemisphere, his bilateral visual disturbance (ring scotoma) might have been accentuated in the contralateral (left) field, as found on the tangent screen. In this connection, it will be recalled that the patient's visual after-images fluctuated and contracted more rapidly in tests of the left eye than in those of the right eye, thus corroborating the foregoing observations.

5 *Tubular Fields*—Centrifugal (outward) motion of targets exposed on the tangent screen led, on the whole, not to the semblance of ring scotoma but to that of a contracted field. Once a certain distance from the point of fixation had been attained, the target became invisible if it was held stationary or moved slowly. This can be understood, again, in terms of a periodic, generalized decrease in excitability of the visual system (fluctuation of the threshold). Rapid motion was appreciated in this peripheral region, so that the contraction of the field (in contrast to the usual hysterical field) was "relative." In other words, the fluctuation indicated that there was a periodic rise in the visual threshold. But this rise was not sufficiently high or continuous to produce a more pronounced and enduring defect in vision, namely, amaurosis in the peripheral field.

6 *The Spinal Field*—The "spiral field" (like the ring scotoma and the tubular field), which was found on examination on the tangent screen under certain conditions, appeared to be an artefact of the method employed in plotting the field of vision. When the target was introduced along each meridian (in a clockwise or counterclockwise order), the field contracted successively, yielding the picture of a spiral. This was due to cumulative effects of continuous stimulation, which, in turn, led to increasing obliteration in the periphery. The spiral was not obtained with other methods of plotting.

#### INTERPRETATION

On the surface, it would seem that certain features in our case could be explained in terms of local effects of fatigue. Thus, fluctuation

and obliteration of visual images were increased by three changes in the procedure of testing (a) prolonging the time of exposure, (b) increasing the degree of eccentricity of the target and/or the distance of the target from the patient and (c) enlarging the area stimulated. Moreover, a spontaneous progressive involvement of the field from the periphery inward, or concentric shrinking, was noted on prolonged exposure of large patterns. This was also found in studies of after-imagery and on examinations with moving stimuli. However, the theory of fatigue is not entirely satisfactory when one considers that recovery of visual function was practically instantaneous on interruption and immediate repetition of any particular test.

We therefore turned to the phenomena of visual extinction for more specific clues. Visual, as well as cutaneous sensory, extinction, we think, is due to a form of rivalry of two or more perceptual processes. This rivalry, which can be demonstrated in the normal person, results in dominance of the stronger, and extinction of the weaker, percept. Such extinction is more apparent in pathologic states, in which the intact or less defective substrate dominates over the more defective substrate.<sup>15</sup> These phenomena were interpreted in the light of the discovery of Dusser de Barenne and McCulloch<sup>29a</sup> that "suppression" in a point in the sensory cortex can be produced by exciting another focus in the same cortical area. In psychologic experiments, Fry<sup>30</sup> found that the image of a flash of light can be "suppressed" by applying another flash of light to adjacent areas of the retina. In orienting our data in terms of extinction, we found that we could explain all the aforementioned features (decrease in function with prolongation of stimulation, etc.) on this basis, rather than on that of fatigue.

Moreover, there are other features in the present case which are in agreement with those previously described in patients who showed extinction in their visual fields.<sup>1b</sup> 1. Tachistoscopic examination failed to bring out any visual defects, while prolonged exposure did. 2. Ring scotoma and tubular fields were found only with slow movement (or prolonged exposure) of targets, rapid movement or brief exposure of targets did not produce such defects in the visual field. 3. Obliteration of images usually started in the periphery of the left lower quadrant, in the region bordering on the absolute (hemicrescent) scotoma, and from there it spread over the whole field. This was

29a Dusser de Barenne, J. G., and McCulloch, W. S. Factors for Facilitation and Extinction in the Central Nervous System, *J. Neurophysiol.* 2: 319-355 (July) 1939.

30 Fry, G. A. Depression of Activity Aroused by a Flash of Light by Applying a Second Flash Immediately Afterwards to Adjacent Areas of Retina, *Am. J. Physiol.* 108: 701-707 (June) 1934.

particularly evident for moving stimuli<sup>31</sup> 4 Double simultaneous stimulation with identical targets to either side of the median line led sometimes to extinction in the left half-field. But this tendency was inconsistent and difficult to interpret because of the continual and irregular fluctuations in different parts of the field.

In the majority of patients observed in our series with visual disturbances, fluctuation and extinction tended to take place in quadrants or half-fields<sup>32</sup>. In the present case the disturbance involved the whole field (although it was most pronounced in the neighborhood of the absolute scotoma). The general involvement of the field produced the semblance of ring scotoma or contracted field with certain methods of plotting. In the act of viewing large patterns, the same general disorder became evident as a gradual "fragmentation" of the patient's field. Even strong configurations, such as concentric circles, were broken up into irregular pieces before they eventually disappeared. This last feature in particular points to the diffuseness of the disturbance in this case. Although a circumscribed lesion in the visual substrate might produce an absolute scotoma surrounded by an area of relative impair-

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31 In this respect, the symptoms shown in this case resemble those observed in 3 other cases in our series. In 1 case, that of a gunshot wound in the right occipitoparietal region near the midline with mild sensory and motor changes in the left lower extremity, no distinct field defects could be demonstrated on the perimeter or the tangent screen. However, with continued exposure of any pattern involving more than the immediate center of the field, the patient complained of a peculiar blacking out, which involved, in succession, three quadrants, leaving intact only one, the right upper homonymous quadrant. The patient then shut his eyes, and his difficulty disappeared immediately, only to reappear after another prolonged (ten to fifteen seconds) exposure. The patient's after-images "decayed" rapidly after first appearing complete, again, this decay took place by way of an almost immediate disappearance of those portions of the after-image which had been exposed to the three involved quadrants. In a similar case, a homonymous defect was noted on the perimeter in the extreme periphery of the right fields, suggesting a late stage in the recovery from an initial right hemianopsia. On the tangent screen, after a few seconds of observation, the whole right half of the field "blacked out," with an illusory inward motion from the periphery to the center. As soon as the patient blinked his eye, the field appeared free again. Such cases of fleeting scotoma, though perhaps related, differ from our present case in that the obliteration occurred in quadrants and half-fields.

32 It is interesting to note that Lashley (*Patterns of Cerebral Integration Indicated by Scotomas of Migraine*, *Arch Neurol & Psychiat* **46** 331-339 [Aug] 1941) postulated slowly progressing "waves" of complete inhibition of visual activity in order to account for the spreading scotomas of migraine.

ment of vision,<sup>33</sup> diffuse lesions produced by head injury (molecular changes in neurons) could implicate the entire visual substrate and field. Such diffuse disturbance would likewise have to account for the occasional difficulties in relative localization in visual space, for the slowing in color perception on the tachistoscope and for the abnormalities of fixation and pursuit. Of particular interest in this connection was the reduction in the threshold for fusion of visual flicker, as well as the patient's difficulty in obtaining good stroboscopic motion, both are consistent with Werner's observations on children with cerebral injury.<sup>34</sup> In experiments with normal subjects, Sanders has shown that prolonged stimulation of a given retinal area "inhibits" stroboscopic motion across this retinal area.<sup>35</sup>

From the foregoing data and interpretations, it is apparent that our patient's visual symptoms were not so bizarre as they first seemed. They showed coherent physiologic patterns and represented a direct, and not a neurotic, response of the organism to the head trauma which had been sustained. This conclusion seems unavoidable despite the fact that we do not know what specific material and physiologic changes in the visual substrate provided the basis for the appearance of increased fluctuation and temporary extinction of images.

In spite of their rarity, these visual disturbances after injury to the brain which (under certain conditions of field taking) manifest themselves as apparent ring scotomas should not be underestimated in their clinical importance. The diffuse, but omnipresent, changes in the visual field can be more incapacitating than more circumscribed scotomas, even to the extent of complete hemianopsia. In the present case, the patient's symptoms persisted, with little improvement, for almost a year after his injury.

#### SUMMARY

After injury to the brain, apparent ring scotomas, concentric contraction of visual fields, shifting and "spiral" fields may be found with

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33 Such areas of relative defect may reach far beyond the scotomatous region. Even focal lesions, apparently, can result in a widespread and systematic distortion of the normal cortical patterning of visual processes. Such dynamic alteration in the topologic projection of the peripheral onto the cortical retina has been assumed by us in cases of micropsia, metamorphosis, teleopsia and specific disturbances in the perception of visual space and motion.

34 Werner, H. and Thuma, B. D. Critical Flicker-Frequency in Children with Brain Injury, *Am J Psychol* **55**:394-399 (July) 1942, A Deficiency in the Perception of Apparent Motion in Children with Brain Injury, *ibid* **55** 58-67 (Jan) 1942.

35 Sanders, E. H. Over den invloed van vermoeden op de optische schijnbewegingen (Uit het fysiologisch laboratorium der Universiteit van Amsterdam), *Nederl tijdschr v geneesk* **65** 1820-1836 1921.

specific methods of examination of the fields. Different types of fields may be encountered in one and the same case. However, the changes observed vary consistently and directly with the different methods of plotting. This is illustrated in a case which was studied with neurologic, psychophysiologic and phenomenologic methods. The unusual field changes (*viz*, ring scotomas and contracted and spiral fields), as well as severe disturbances in visual perception (haziness, fragmentation and obliteration of images from the periphery inward), seemed to be produced by a continual fluctuation in the visual threshold for different parts of the field, with concomitant phenomena of extinction. It is concluded that such ring scotomas, despite their variability, have an "organic" basis, as pointed out by Goldstein in 1927.

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## Correspondence

### CAMPTOCORMIA

*To the Editor*—In the discussion on the article entitled "Camptocormia A Functional Condition of the Back in Neurotic Soldiers," by Lieut Col S A Sandler, an abstract of which was published in the February 1946 issue of the ARCHIVES, page 158, it is stated (column 2, line 5 of the discussion)

"As is generally known, the term camptocormia was coined by Babinski after the last war, he was fond of Greek derivations. In the same volume in which he described camptocormia, he described pithiatism—his term for suggestion neurosis. He is also responsible for the term adiadokokinesis."

It is true that Babinski was fond of Greek derivations and introduced the term adiadokokinesis, but he did not coin the term camptocormia. Without using this special term, A Souques described this syndrome in soldiers at a meeting of the Société de Neurologie de Paris Feb 18, 1915, under the title "Contractures ou pseudo-contractures hystéro-traumatiques" (*Rev neurol* 22:430, 1914-1915). The term camptocormia appears for the first time in an article by Souques and Rosanoff-Saloff (*La campocormie*, *Rev neurol* 22:937, 1914-1915). Here, it is said "*L'un de nous, M Souques, propose de donner à cette incurvation le nom de camptocormie*" In an article by Rosanoff-Saloff (*Considérations générales sur la camptocormie*, *Nouv iconog de la Salpêtrière* 28:28, 1916-1917) it was stated "*Le terme de camptocormie donné par M Souques à ces attitudes est plus exact*" Hysterical kyphosis after trauma had been known long before Souques, as Brodie's disease, from the latter's description in 1879-1880 (Deléarde *De la cyphose hystéro-traumatique* [maladie de Brodie] *Gaz d hôp* 75:749, 1902).

R WARTENBERG, M D, San Francisco

University Hospital (22)



# News and Comment

## THE AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY, INC

The following candidates successfully passed the examinations of the American Board of Psychiatry and Neurology, Inc, held at San Francisco, June 25, 1946, and have been certified

*Psychiatry* — Alfred Auerback, San Francisco, Lindsay Eugene Beaton, Tucson, Ariz, O L Bendheim, Phoenix, Ariz, Major Robert A Coen, M C, A U S, Bernard L Diamond, San Francisco, Floyd Oliver Due, Oakland, Calif, Malcolm Hedges Finley, San Francisco, Edward Earle Hause, San Francisco, Roy Sears Hubbs, Palo Alto, Calif, Stephen Elliott Kramer, Pueblo, Colo, Richard Hooker Lambert, San Mateo, Calif, David Washington Lester, San Diego, Calif, Col Emmett B Litteral, M C, U S A, Richard D Lowenberg, San Francisco, John Morgan Lyon, Denver, John D Moriarty, Vallejo, Calif, Herbert Allen Perry, Medical Lake, Wash, Lieut Col Donald B Peterson, M C, U S A, David G Schmidt, Larkspur, Calif, Capt Earl J Simburg, M C, A U S

*Neurology* — Clemson Marsh, Los Angeles, Herman Michael Rosow, Los Angeles

*Psychiatry and Neurology* — Elnor R Ives, Los Angeles, Henry W Newman, San Francisco, Charles G Polan, Seattle, Maier I Tuchler, San Francisco

Certification in psychiatry and neurology has been given on record to Isham Kimbell, Fort Custer, Mich

## AMERICAN SOCIETY FOR RESEARCH IN PSYCHO- SOMATIC PROBLEMS, INC

At the third annual meeting of the American Society for Research in Psychosomatic Problems, Inc, held in New York, May 11-12, 1946, the following officers were elected Adolf Meyer, M D, honorary president (continued), Edward Weiss, M D, president, and Edwin G Zabriskie, M D, secretary-treasurer (continued)

Council members appointed were William Dock, M D, Flanders Dunbar, M D (continued), Roy G Hoskins, M D, Jules Masserman, M D (continued), Elizabeth Healy Ross (continued), Leonard G Rowntree, M D (continued), Leon Saul, M D, Milton J E Senn, M D (continued), George Soule, and J Murray Steele, M D

## MAJOR HARRY L FREEMAN AWARDED ARMY COMMENDATION RIBBON

The Transportation Corps Center, Fort Eustis, Va, is proud to announce that Major Harry L Freedman, Medical Corps, Army of the United States, presently the director of the Mental Hygiene Unit here, and recently awarded the Legion of Merit, has just been awarded the Army Commendation Ribbon by the War Department, United States Army, and by direction of the Secretary of War was authorized to wear that ribbon

His citation for the Army Commendation Ribbon, received from Major General H C Ingles, U S A, Chief Signal Officer, United States Army, reads

"Major Freedman as Director, Mental Hygiene Unit, Headquarters, Eastern Signal Corps Unit Training Center, Fort Monmouth, New Jersey, from 22 December 1941 to 22 November 1943, capably discharged important responsibilities in the organization and operation of a Psychiatric Unit for the reclassification and elimination of maladjusted soldiers"

# Abstracts from Current Literature

EDITED BY DR BERNARD J ALPERS

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## Physiology and Biochemistry

VERTICAL NYSTAGMUS PRODUCED BY PERIPHERAL LABYRINTHINE LESIONS E A SPIEGEL and N P SCALA, Arch Otolaryng **40** 160 (Sept) 1944

Vertical nystagmus is generally considered one of the most important signs in arriving at a differential diagnosis between a lesion of the peripheral labyrinth and a lesion of its central nuclei and pathways. Usually it appears almost exclusively with lesions of the latter type, and it is exceptionally rare with lesions restricted to the vertical canals. Spiegel and Scala observed vertical nystagmus in cats after bilateral puncture of the round window. It was present in 5 of 10 animals, in 1 cat oblique nystagmus appeared, while in the others transitory horizontal undulation of the eyeballs or weak horizontal nystagmus followed the operative procedure. The vertical nystagmus usually was directed toward the upper lid and had a frequency of from 5 to 100 per minute. The vertical nystagmus is thought to be an expression of irritation produced by the escape of perilymph. In later stages following puncture of both round windows, definite symptoms of hypofunction of labyrinthine receptors were found. Similar symptoms may also be noticed after puncture of one of the round windows. Puncture of a round window in cats also induces hypofunction of the maculas, although such an effect may remain unnoticed in otherwise normal animals and may be demonstrated by special methods only. One of these methods is the induction of catalepsy with bulbocapnine.

A different type of vertical nystagmus was observed in further experiments, in which gradually developing paralysis of the labyrinth followed the injection of cocaine hydrochloride into the tympanic cavity. The solution of cocaine diffusing into the inner ear produced signs of labyrinthine paralysis.

The authors believe that the mechanism of these phenomena possibly is that of release of receptors in the semicircular canals from a dampening influence normally originating in the maculas, through partial paralysis of the latter.

RYAN, Philadelphia

THE RELATIVE POTENCY OF SOME ADRENAL CORTICAL STEROIDS IN THE MUSCLE-WORK TEST DWIGHT J INGLE and M H KUIZENGA, Endocrinology **36** 218 (March) 1945

New data are presented to show that the decreased ability of adrenalectomized rats to work is due to adrenal cortex insufficiency and not to operative shock. The study was carried out with the purpose of comparing the effects of various biologically active adrenal cortex steroids on the ability of adrenalectomized rats to work. As the study was carried out, it was found that 17-hydroxycorticosterone was the most active compound, 17-hydroxy-11-dehydroxycorticosterone was second, corticosterone was third, and 11-desoxycorticosterone was much less active than any of the C-11-oxygenated compounds.

PALMER, Philadelphia

THE METABOLISM OF ACETALDEHYDE WITH ACETOIN FORMATION E STOTZ, W W WISTERFELD and R L BERG, J Biol Chem **152** 41, 1944

Acetaldehyde is a primary product of alcohol metabolism in the animal body. Together with alcohol, it comprises the equilibrium system activated by the alcohol dehydrogenase system, and its concentration in the blood, particularly in man, rises many fold after administration of alcohol. For this reason it merits

attention, but it is probably of further importance in the general scheme of carbohydrate metabolism. Stotz, Westerfeld and Berg found that acetaldehyde is metabolized when incubated with rat brain homogenates. Its rate of disappearance is greatly accelerated by addition of pyruvate and further increased by addition of diphosphothiamine. Disappearance of pyruvate is also accelerated by the addition of acetaldehyde, but the effect is not so pronounced, owing to an initially high rate of pyruvate metabolism. Acetoin (2-butanone-3-hydroxyacetylmethylcarbinol) is formed nearly quantitatively in rat brain homogenates from acetaldehyde in the presence of pyruvate. The same factors which accelerate disappearance of acetaldehyde also increase formation of acetoin. Brain tissue from thiamine-deficient pigeons shows a notably lower ability to form acetoin from acetaldehyde and pyruvate and is stimulated in this respect to a greater extent than normal pigeon brain by diphosphothiamine. Certain toxic manifestations of acetaldehyde in rats are described, and a procedure was developed whereby formation of acetoin from acetaldehyde was demonstrated *in vivo* by the appearance of acetoin in the blood.

PAGE, Cleveland

THE CREATINE AND CREATININE EXCRETION OF NORMAL ADULT MALES. ANTHONY A. ALBANESE and DOROTHY M. WANGERIN, *Science* **100** 58 (July 21) 1944

Albanese and Wangerin report their observations on creatine and creatinine excretion in 30 normal adult male subjects studied for thirty-eight to sixty days under normal and experimental dietary conditions. Individual daily variations of 10 to 25 per cent of the total creatinine excreted were observed. However, the creatinine excretion was relatively constant under tremendous variations in the protein intake. The irregularities in creatinine excretion are greater than heretofore assumed, and variations in creatinine output are not necessarily indicative of inaccurate twenty-four hour collection of urine.

A simple modification of the Folin method for determining creatine is described. This technic reveals considerable quantities of creatine that may be present in urine but not detectable with the Folin technic.

The authors' data indicate that creatinuria in the adult male is a normal process, and not a feminine or prepuberal male characteristic.

GUTTMAN, Philadelphia

## Psychiatry and Psychopathology

THE NEUROTIC CONSTITUTION. ELIOT SLATER, *J. Neurol. & Psychiat.* **6** 1 (Jan-April) 1943

Slater made a statistical study of 2,000 neurotic soldiers admitted to one E.M.S. neurosis center. The patients were classified under organic states, head injury, epilepsy, schizophrenia, endogenous depression, mental defect, psychopathic personality, anxiety neurosis, hysteria and reactive depression and into the smaller groups of obsessional neurosis, enuresis and malingering. The various diagnostic groups showed no significant differences with respect to age or religion. The mentally defective patients and patients with endogenous depressions came predominantly from the group of unskilled laborers, and the schizophrenic patients, from sedentary occupations. The frequency of noncommissioned officers was highest in the categories of the obsessive neuroses and the endogenous and reactive depressions. There was a general predominance of the asthenic constitution, while the pyknic habitus was most frequent in the manic-depressive group. An "inhibited" sexual drive was common in all groups, but especially in the mentally defective and psychopathic patients. In 55.7 per cent of the patients there was a positive family history of psychiatric deviation. In 58.8 per cent there was some degree of neurosis in childhood. Almost a quarter of the patients had had previous nervous breakdowns, two thirds of the patients with endogenous depressions having such a history. An abnormal premorbid personality was present in over 40 per

cent of the whole group, especially in schizophrenic patients. The most common abnormal personality traits were undue lability of mood and unsociable and anergic tendencies. A third of the patients were of poor intelligence, and there was a frequent association between subnormal intelligence and hysteria. Preconditioning in the form of a bad environment was especially a factor in the neuroses. Previous service in the Army was high. Among the most common precipitating factors were military stress, separation from family, home worries and physical ill health. These factors were elicited in 50 per cent of patients, especially those with anxiety neuroses. They were insignificant in the other 50 per cent, which was comprised chiefly of patients with schizophrenia, epilepsy, psychopathy, mental deficiency and the organic states. Head injury was significantly high in cases of epilepsy, and various physical handicaps were commonly associated with the neuroses. Anxiety states were usually of more recent origin, while some disorders, such as psychopathic personality, were of long duration. Patients of the latter type might have been kept out of the Army through more adequate screening. The most common and least specific symptoms were depression, anxiety and hypochondriasis, while obsessions were rare and were usually associated with depressive reactions. In patients with neuroses the symptoms were fluid and interchangeable. Nearly 60 per cent of the patients received no specific therapy, treatment being limited by the frequency of low intelligence and constitutional instability and by working conditions. Psychotherapy was used with about one fifth of the patients, and narcosis with about 5 per cent (patients with anxiety neurosis), insulin coma therapy was employed with 18 per cent of schizophrenic patients and with those showing considerable loss of weight. Complete recovery occurred in about 10 per cent, and this number together with the patients showing great improvement comprised 25 per cent of the total series, while three fourths of the patients had to be invalided. Of the number of the latter returned to duty half had a relapse. The highest rates of recovery were obtained among patients with organic states, head injury, anxiety neurosis, hysteria and depression, in that order. The chief prognostic criterion consisted in signs of constitutional instability. A poor prognosis was associated with an asthenic habitus, a positive family history of psychiatric deviation, neurosis in childhood, abnormal personality traits, poor intelligence, unsatisfactory home conditions and a duration of illness exceeding two years. A definite inverse ratio was found between different degrees of constitutional abnormality and resistance to military stress.

The study indicated that the organic state is largely independent of the individual constitution and is mainly dependent on the exogenous factor. In the endogenous states the hereditary disposition was all important. In the neuroses, while the exogenous stress was important, the reaction was principally determined by the constitutional predisposition. The neurotic state, according to the author, is merely an exacerbation of the type of response characteristic of the particular patient. The individual constitution of the neurotic patient determines the form and severity of the symptoms, while the environment controls the time of their manifestation. This neurotic constitution and an inadequate intellectual endowment are the two most important predisposing factors in the nervous breakdown.

MALAMUD, San Francisco

### Diseases of the Spinal Cord

INTERVERTEBRAL DISK INJURY ANALYSIS FROM AN INDUSTRIAL STANDPOINT.  
H. C. MARBLE and W. A. BISHOP, *J. Indust. Hyg. & Toxicol.* 27:103 (April) 1945.

Marble and Bishop attempt to present impartially some of the facts relating to injury of the intervertebral disk from the standpoint of an industrial surgical clinic. The sources of the material are the records of one of the largest insurance companies in the United States interested in workmen's compensation. The facts

as gathered represent a cross section of the work of both neurosurgeons and orthopedic surgeons throughout the country. Compensable cases represent probably the most important group, since injury to the back in industry is frequent and the results of therapy vital to the future of the patient. Of 496 industrial patients suspected of having sustained herniation of the intervertebral disk, 92 or approximately one fifth, were operated on, while four fifths received other therapy. The 92 cases are analyzed from the standpoint of cost, disability, cause and diagnostic criteria. In less than 50 per cent of cases the result is favorable.

J A M A

#### LESIONS OF CERVICAL INTERVERTEBRAL DISK J BROWDER and R WATSON, New York State J Med 45 730 (April 1) 1945

From a review of the literature, Browder and Watson collected only 69 verified cases of protrusion or herniation of a part of the cervical disk. In this paper they present their experiences with 22 cases in which this lesion had disturbed the function of the cervical portion of the spinal cord and/or nerve roots. In 21 cases the diagnosis was verified at operation and in 1 at necropsy. Three different types of pathologic processes were encountered: (a) discrete, oval or rounded nodules projecting into the ventral vertebral canal, (b) true dorsal herniations of the nucleus pulposus, and (c) ridges of annulus fibrosus surmounting hypertrophic bone at the margins of the adjacent vertebra. A negative reaction to the Queckenstedt test does not exclude the presence of such a lesion. The operative mortality for the series was zero. One patient died before coming to operation.

J A M A

#### PRESENT STATUS OF SURGICAL TREATMENT OF SCIATIC AND LUMBOSCIATIC PAIN DUE TO LESIONS OF THE INTERVERTEBRAL DISKS GERMAN HUGO DICKMANN, Prensa med argnt 32 691 (April 20) 1945

Twenty-one verified cases of herniated disk are reported from the Rawson Hospital in Buenos Aires. The author advises exploration of the fourth and fifth lumbar intervertebral disks in all cases. If the pain radiates to the anterior aspect of the right thigh, the third lumbar intervertebral disk should also be explored. The laminectomy should be as limited as possible. The lower spine should be stabilized if necessary by fusion. A proper corset should be worn for three or four months after operation. The author does not use myelography routinely unless the total protein of the spinal fluid is 80 mg per hundred cubic centimeters or over. In only 1 of the 21 cases was such a high protein content noted. Negative myelographic evidence does not exclude the presence of a lesion of the disk. There was actual herniation in one third of the cases, in two thirds the disk was concealed. There were 16 males and 5 females in the series. Sixteen were between 21 and 40 years of age, 1 was 19, 3 were between 41 and 50, and 1 was between 51 and 60. In 12 cases the pain was on the left side, in 8, on the right side, and in 1 it was bilateral. In 16 cases only one disk was involved, and in 3 cases the fourth and fifth lumbar disks, and in 2 cases the third, fourth and fifth lumbar disks were involved. The ankle jerks were absent in 4 cases and diminished in 4 cases, the knee jerks were absent bilaterally in 1 case, the ankle and knee jerks on the same side were not elicited in 1 case, in 2 cases the knee and ankle jerks were not obtained on either side. There were no sensory changes in 15 cases. There was hyperesthesia over the outer aspect of the foot in 4 cases, and in 2 cases hyperesthesia was found on the lateral aspect of the foot and the anterolateral aspect of the leg. There was complete recovery in 10 cases, in 10 cases there was definite improvement. In 1 case sciatic pain recurred seven months after the operation. Section of the fourth lumbar nerve root was done, and the pain disappeared.

SAVITSKY, New York

## Peripheral and Cranial Nerves

MODERN VIEW OF NEURALGIA REFERABLE TO MECKEL'S GANGLION B R DYSART,  
Arch Otolaryng 40 29 (July) 1944

Dysart cocaineized the sphenopalatine ganglion in 3 cases of corneal ulcer associated with pain. In all instances the pain was relieved, usually within four to five minutes after cocaineization. In 2 of the cases there were multiple ulcers, some of which healed. Pain was relieved, but no improvement was noticed in the appearance of the ulcer in the other case. Relief of pain was temporary, and the procedure had to be repeated at various intervals.

The use of the proper technic is important. When a patient is being treated for the first time and his tolerance to cocaine is not known, one must proceed with care. A small amount of 2 per cent cocaine hydrochloride is sprayed into the middle meatus, and a few minutes later the pulse rate is checked. If there is no elevation, 1 drop of 10 per cent cocaine hydrochloride is applied by means of a fine, flexible copper applicator. This is left in place for five minutes. The turbinates should be shrunk thoroughly with a vasoconstrictor drug before an attempt is made to reach the ganglion. One or two puffs of 2 per cent cocaine hydrochloride directed toward the middle turbinate usually produces the desired result. Then, with the tip turned up, the applicator is slid along the lower edge of the middle turbinate without touching it or the septum, if possible. As the posterior wall of the nose is reached, the tip is rotated outward and lifted upward to lie just back of the attachment of the middle turbinate. If no improvement results, a saturated solution of cocaine hydrochloride (90 per cent) is used and is applied for five minutes. At any rise of pulse rate or complaint of the patient's feeling a little faint, the treatment is stopped.

The author believes that cocaineization of the sphenopalatine ganglion probably achieves its effects by intercepting nerve impulses, and not by influencing any pathologic process in the ganglion.

RYAN, Philadelphia

PRESENT STATUS OF DIAGNOSIS AND MANAGEMENT OF MENIERE'S SYNDROME  
HANS BRUNNER, Arch Otolaryng 40 38 (July) 1944

Meniere's syndrome, according to recent studies, is due to an acute increase of fluid within the internal ear, particularly within the endolymphatic canal of the inferior part of the internal ear. In a typical attack the patient complains of tinnitus, diminished auditory acuity and vertigo. The vertigo is of labyrinthine type. Only vertigo of the type which can be produced by the usual clinical methods of examining the labyrinth should be considered as labyrinthine. Labyrinthine dizziness, which lasts for a certain period and reaches a high degree of intensity, is always accompanied with spontaneous nystagmus. Typical attacks are often followed by what the author calls a Meniere neurosis. This, however, does not present spontaneous nystagmus, and if the latter is found between Meniere attacks it should not be thought of labyrinthine origin but, rather, should be considered indicative of a lesion of the posterior fossa. The evaluation of symptoms becomes difficult when the patient complains only of dizziness or only of tinnitus and deafness. In such instances a definite diagnosis cannot be made until the patient is under observation for a long period.

The cause of Meniere attacks and of Meniere's syndrome may be systemic, cerebral or aural. The syndrome is then called "symptomatic Meniere's syndrome." When no cause can be determined, the condition is designated as "idiopathic Meniere's syndrome." Cases of idiopathic Meniere's syndrome are in the minority, but they have stimulated great interest concerning the cause of the disorder. At present two theories prevail: (1) the metabolic theory and (2) the vascular theory. The metabolic theory is not supported by microscopic study of the human ear by chemical examination of the blood or by the results of treatment. The vascular theory propounded by Meniere is supported by micro-

scopic observations on the human ear, as well as by experiment, and explains the pathologic picture of the idiopathic, as well as the symptomatic, Meniere syndrome. Most frequently the angioneurotic disturbance within the internal ear is due to cerebral arteriosclerosis. Incipient arteriosclerosis of the brain should be considered in every case of Meniere's syndrome in which the first attack takes place between the third and the fifth decade of life and in which there is no evidence of other etiologic factors.

Among the systemic diseases, syphilis, malaria, influenza, the leukemias and virus infections may cause the symptomatic Meniere syndrome. Infrequently, some allergic process may be responsible. A chronic adhesive process of the tympanic cavity is frequently found to produce the symptomatic Meniere syndrome.

Meniere neurosis should always be excluded. When the syndrome is symptomatic, the underlying condition should be treated. There is no satisfactory treatment for the idiopathic Meniere syndrome. If the diagnosis of Meniere syndrome is certain, surgical intervention is indicated only when conservative measures have proved unsuccessful and when the disease is progressive on one side while the other ear is normal.

RYAN, Philadelphia

#### PSEUDOMEMBRANOUS ANGINA FOLLOWED BY PARTIAL PHARYNGEAL PARALYSIS JOSEPH V. M. ROSS, Arch Otolaryng 40 164 (Sept) 1944

Ross reports 2 cases of Vincent's (pseudomembranous) angina complicated with late partial pharyngeal paralysis in young German prisoners of war. On admission to the hospital the patients complained of headache, malaise, nausea, sore throat and difficulty in swallowing. The signs were those of Vincent's angina of a severe type, with typical lesions in the throat, dysphagia, fetor oris and submaxillary lymphadenopathy. There was no obvious involvement of the gums. Organisms of Vincent's angina were found in the smears of material taken from the throats. Culture of the same material showed no diphtheria bacilli. With the usual treatment for Vincent's angina, the lesions of the throat disappeared. After being discharged from the hospital, both patients were seen in the clinic within a week. They had had the same complaints: difficulty in phonation, with a nasal twang to the voice, and difficulty in swallowing both solids and fluids, the former causing pain in the throat and the latter causing nasal regurgitation with cough. These symptoms developed fifteen and twenty-three days, respectively, after the original illness. Examination revealed left-sided pharyngeal palsy associated with anesthesia in both cases. With vitamin B complex therapy slow progress was observed.

RYAN, Philadelphia

#### A TYPE OF NEURITIS ASSOCIATED WITH MALARIAL FEVER ABNER M. HARVEY, Bull Johns Hopkins Hosp 75 225 (Oct) 1944

Harvey discusses a type of peripheral neuritis which occurs in association with malaria. It is characterized by pain, hyperesthesia and hyperalgesia, increased sweating and a feeling of tightness, with increase in muscle tone accompanied by actual muscular contractions. In cases of the mild form the only abnormalities are transient attacks of numbness and tingling. There is considerable variation in the time of onset of the first neurologic symptoms in relation to the febrile paroxysm.

Of 100 consecutive cases of malaria, symptoms of the milder type alone, without objective neurologic abnormalities, were present in 18 per cent. Harvey observed 16 cases of the more severe type of neuritis.

GUTTMAN, Philadelphia

#### REVIEW OF ONE HUNDRED CASES OF DIABETIC NEUROPATHY A. RUDY and S. H. EPSTEIN, J Clin Endocrinol 5 92 (Feb) 1945

Rudy and Epstein review 100 cases of diabetic neuropathy followed from one to ten years. The incidence according to clinical localization was as follows:

neuritis, 54 cases, myelopathy, 26 cases, encephalopathy, 4 cases, encephalomyelopathy, 5 cases, and neurogenic disturbances of the bladder, 11 cases. Diabetic neuropathy is a generalized neurologic disturbance. It is observed not only in the acute stage of diabetes but also soon after the control of the glycosuria and hyperglycemia and with chronic, and even mild, diabetes. This neuropathy develops most frequently in patients over 50 years of age and is preceded or accompanied by considerable loss of weight. Symptoms and signs of a vitamin B complex deficiency are frequently associated with it. The vitamin deficiency is secondary, and it appears to be caused by the disturbed metabolism and at times by an associated chronic infection or other complication. A demonstrable dietary insufficiency is a factor only in certain cases. Complete recovery from the neuropathy is uncertain and slow, but it occurs after prolonged therapy with vitamin B and control of the glycosuria and hyperglycemia.

J A M A

### Vegetative and Endocrine Systems

EFFECTS OF ADRENOCORTICOTROPIC HORMONE ON THE OSSEOUS SYSTEM IN NORMAL RATS. HERMANN BECKS, MIRIAM E. SIMPSON, CHOH HAO LI and HERBERT M. EVANS, *Endocrinology* **34** 305 (May) 1944.

The authors have shown that by treating normal rats with a preparation of the adrenocorticotrophic hormone both chondrogenesis and osteogenesis are retarded, whereas osteogenesis ceased in hypophysectomized rats. Although lessened food consumption was shown to result in retardation of gain in body weight and bone growth, it did not explain the extent of the retardation in the animals treated with the adrenocorticotrophic hormone. In the absence of the adrenal glands, there was shown to be no significant changes in bone or growth inhibition.

PALMER, Philadelphia

ANTAGONISM OF PITUITARY ADRENOCORTICOTROPIC HORMONE TO THE ACTION OF GROWTH HORMONE ON THE OSSEOUS SYSTEM OF HYPOPHYSECTOMIZED RATS. HERMANN BECKS, MIRIAM E. SIMPSON, WALTER MARX, CHOH HAO LI and HERBERT M. EVANS, *Endocrinology* **34** 311 (May) 1944.

After hypophysectomy, the proximal epiphysial regions of the tibias of rats were compared when no injections were given and after injections of the adrenocorticotrophic hormone of the pituitary, the growth hormone and a combination of the two. The results observed showed that the adrenocorticotrophic hormone of the pituitary given alone scarcely affected the inactive condition of the epiphysis, the state of the bone formation was characteristic and similar to that of the controls. The growth hormone activated the cartilage and caused resumption of formation of delicate, straight trabeculae of bone. Simultaneous injection of adrenocorticotrophic hormone and growth hormone produced (1) a great decrease in width of the proximal epiphysial cartilage, (2) significant retardation of endochondral bone formation and (3) great decrease in osteoblastic and osteoclastic activity.

PALMER, Philadelphia

CUSHING'S SYNDROME WITHOUT ADENOMATOUS OR HYPERPLASTIC CHANGES IN PITUITARY BODY OR ADRENAL CORTICES AND COMPLICATED BY ALKALOSIS. REPORT OF CASE WITH NECROPSY. H. E. CLUXTON JR., W. A. BENNETT, M. H. POWER and E. J. KEPLER, *J. Clin. Endocrinol.* **5** 61 (Feb) 1945.

Cluxton and his associates report the clinical history and necropsy observations in the case of a woman aged 27 who came to the Mayo Clinic presenting most of the features of Cushing's disease (pituitary basophilism). The absence of adenomas or neoplastic or hyperplastic changes in the pituitary body, thymus or adrenal cortex and the associated alkalosis that was present during the life of the patient are elements of additional interest. The patient's illness could not be



attributed to any demonstrable anatomic abnormality if one expects the hyaline changes that were found in the basophilic cells of the anterior lobe of the pituitary body. The physiologic significance of these changes is not known, but one of the authors believes that these changes are secondary or retrograde rather than an alteration of fundamental significance in the causation of the syndrome and that the clinical manifestations of the patient's illness were an expression of an abnormal function of the adrenal cortex of a hypersecretory character in spite of the fact that there was no histologic evidence to support this view. This case also presents one more instance of alkalosis and low potassium content of the blood occurring with Cushing's syndrome, 3 cases having previously been reported from the Mayo Clinic. In some cases alkalosis occurs solely as the result of abnormal function of the adrenal cortex.

J A M A

CUSHING'S SYNDROME EVELYN ANDERSON and WLBH HAYMAKER, *J Nerv & Ment Dis* **99** 511 (May) 1944

Anderson and Haymaker review the controversy as to the pituitary or the adrenocortical origin of Cushing's syndrome. They believe that the demonstration of a substance resembling the hormone of the adrenal cortex in the blood and urine of patients with the disease is evidence of its adrenocortical nature. They report 7 cases of the syndrome. In 4 cases death ensued, and in 3 cases improvement was observed. The occasional cyclic nature of the disease is illustrated in 2 of the cases, in which spontaneous remission occurred. In 2 cases the hair of the scalp changed from blond to black, and in 1 case became coarse. Studies of blood electrolytes revealed that the levels of potassium and sodium in the serum varied from time to time in the same patient, but in some of the cases the serum potassium tended to be at the lower range of normal. This observation may possibly be considered significant as an expression of an excess of adrenocortical hormone. In 2 cases significant amounts of adrenocortical hormone were found in the blood and urine, and in another case the hormone was demonstrated in the urine alone. The adiposity and hypertension which invariably occur with Cushing's syndrome may be due to the effects of the hormone of the adrenal cortex rather than of the androgenic fraction. Albright designated the former as the S hormone and the latter as the N hormone.

CHODOFF, Langley Field, Va

### Treatment, Neurosurgery

SULFADIAZINE AND ITS SODIUM COMPOUND IN TREATMENT OF MENINGOCOCCIC MENINGITIS AND MENINGOCOCCEMIA EMANUEL APPELBAUM and JACK NELSON, *Am J M Sc* **207** 492 (April) 1944

Appelbaum and Nelson treated 142 patients with meningococcic meningitis by means of sulfadiazine and its sodium compound. One hundred and twenty-six of the 142 patients were treated within the first three days of illness, 115 patients showed definite changes in the mental state, varying from irritability and apathy to delirium and coma. Ninety-two patients had hemorrhagic eruption.

The cerebrospinal fluid showed varying degrees of turbidity, with predominance of polymorphonuclear cells. The sugar was either absent or greatly diminished in almost all patients. The smears of 123 patients showed varying numbers of intracellular and extracellular gram-negative diplococci. In 95 patients the organisms were found both by smear and by culture. The strain of meningococcus was identified in 99 instances of meningitis and in the 8 cases of meningococcemia without meningeal involvement.

On the first day of treatment, children under 1 year of age received from 2 to 3 Gm of the drug, children from 1 to 3 years of age received from 3 to 4 Gm, children above that age received from 4 to 7 Gm, and adults, from 9 to 12 Gm. In 89 instances the drug was given intravenously during the first twelve to twenty-four hours, as a rule in a 5 per cent solution in distilled water. Prompt and con-

sistent results were obtained with levels of the drug ranging from 10 to 15 mg per hundred cubic centimeters in the blood and from 7 to 10 mg per hundred cubic centimeters in the cerebrospinal fluid

The patients showed striking clinical improvement on the second or third day of chemotherapy. It was found that chemotherapy might be discontinued after the patient had been afebrile for twenty-four to forty-eight hours and had received a total of 15 to 20 Gm of the drug. In the fulminating form of the disease, the outstanding clinical feature was the presence of circulatory collapse.

Arthritis occurred in 15 patients. The low incidence of serious complications was remarkable. Toxic reactions due to sulfadiazine were encountered in 42 of the patients. Hematuria was observed in 20 patients. It is necessary to maintain a urinary output of at least 1,200 cc in each twenty-four hour period.

Drug fever, noted 15 times, was the second most important toxic effect. In 4 cases drug intoxication produced the syndrome of encephalopathy, in which the clinical picture was characterized by varying grades of stupor, often progressing to deep coma. There were only 2 instances of peripheral neuropathy. The presence of initial leukopenia is not a contraindication to the use of chemotherapy.

The authors believe that there is little advantage to be expected from the additional use of the specific serum.

MICHAELS, M C, A U S

#### AMPHETAMINE SULFATE IN ABORTING THE ACUTE ALCOHOLIC CYCLE MICHAEL M MILLER, *Am J Psychiat* **100** 800 (May) 1944

Miller studied the effects of amphetamine sulfate during the period following acute intoxication in 56 nonpsychotic patients with chronic alcoholism. The medical regimen consisted in the administration of 10 mg of amphetamine sulfate after breakfast and lunch, 0.1 Gm of phenobarbital on retiring and 30 to 40 mg. of thiamine hydrochloride per day. In 49 patients the drinking cycle was interrupted. In 8 control patients who received placebos the drinking cycle was not disturbed. Single doses of amphetamine sulfate given to semistuporous patients roused them. "Hang-over effects" were greatly reduced. The treatment resulted in improvement of mood, rapport, awareness, sensory perception and activity drive.

FORSTER, Philadelphia

#### THROMBOSIS OF THE CAVERNOUS SINUS WITH HEMOLYTIC STREPTOCOCCIC BACTERMIA JONAS W WOLF, *Arch Otolaryng* **40** 33 (July) 1944

Wolf reports recovery in a case of thrombosis of the cavernous sinus. The patient was a 10 year old boy, and the source of the infection was a furuncle on the bridge of the nose. Associated with the thrombosis were hemolytic streptococcemia and multiple renal and pulmonary thrombi. Over a period of nineteen days the child received 64 Gm of sulfadiazine and 500,000 Oxford units of penicillin. Therapy was instituted with the administration of sodium sulfadiazine intravenously and of sulfadiazine by mouth. When no change in the patient's condition developed, the sulfadiazine was discontinued and a dose of 60,000 units of penicillin was given intravenously by the continuous drip method. No improvement was noted, and on the fourth day of treatment the patient received 5 Gm of sodium sulfadiazine and 60,000 units of penicillin intravenously. Use of the two drugs simultaneously brought about complete recovery in the following two weeks.

RYAN, Philadelphia

#### NEW ASPECTS OF SPINAL INJURIES A G DAVIS, *Arch Surg* **46** 619 (May) 1943

In the treatment of spinal fractures and dislocations the following points have been generally accepted. 1 Hyperextension is generally applied for the reduction of fractures. 2 The fractured vertebral body may be depended on to form a callus, as does any other broken bone. 3 In cases of injury to the cord, laminectomy as

a decompressive procedure occupies a place distinctly secondary to that of hyperextension 4 The Queckenstedt test is an important aid in determination of the presence of subarachnoid block before and after hyperextension 5 Skeletal traction by means of the Crutchfield clamp is the best method of treatment for crush fractures and fracture dislocations of the cervical region 6 The intact posterior arches are capable of bearing the weight of the torso without the aid of the vertebral body, hence it is safe for the patient to be ambulatory for part of the period of convalescence 7 The anterior longitudinal ligament acts as the main reducing medium and as the chief check strap opposed to excessive hyperextension

There is some disagreement as to the period of convalescence and the method of reduction in cases of compression fracture The author keeps his patients in the recumbent position for six weeks and then permits them to be ambulatory in a hyperextension cast for another six weeks In cases of thoracolumbar fractures reduction can best be obtained by the foot suspension method

Fractures of the laminae, pedicles and articular facets often are not recognizable in roentgenograms In certain cases of fracture with "locked" dislocation the roentgenographic picture is characteristic Recognition of these cases is important, because the lesion should not be manipulated but should be treated by open reduction after the dislocation has been "unlocked" in a flexion device

Since the tensile strength of the anterior longitudinal ligament is great (breaking point, 153 Kg) and the pull needed for reduction rarely exceeds 36 Kg, there is an ample margin of safety

A method is described for correction of bilateral cervical dislocation Certain types of anterior cervical dislocation can easily be corrected in the early stage by a hyperextension collar, if neglected, the dislocation may be progressive and require fusion operation

LIST, Ann Arbor, Mich

AMPHETAMINE (BENZEDRINE) SULFATE UPON HIGHER NERVOUS ACTIVITY COMPARED WITH ALCOHOL NATHANIEL FINKELSTEIN, E BRUCE ALPERN and W HORSLEY GANTT, Bull Johns Hopkins Hosp 76 61 (Feb) 1945

Finkelstein, Alpern and Gantt studied the effect of amphetamine sulfate and alcohol on a group of 19 subjects They observed that amphetamine sulfate in oral doses of 10 to 15 and 20 to 30 mg increased the systolic and diastolic blood pressures of healthy young adults (an average of 136 mm for the systolic and of 104 mm for the diastolic pressure) It did not alter the pulse rate The resting respiratory rate was increased about 21 per cent The drug had an effect on motor conditioned reflexes, causing slight improvement in differentiation between positive and negative conditioned stimuli The threshold of sensation to an electrical shock, the acuity of hearing and the performance with a number series problem test were unchanged by amphetamine

The presence of a respiratory conditioned reflex under these experimental conditions was observed

Alcohol had a more pronounced effect on motor conditioned reflexes than amphetamine Alcohol favored excitatory reactions, interfered with inhibition and tended to convert inhibitory into excitatory reactions, impaired the respiratory conditioned reflexes and greatly increased the threshold for perception and for pain

The authors conclude that the conditioned reflex test was more sensitive in detecting a change in higher functions of the nervous system than were the verbal tests which were used

GUTTMAN, Philadelphia

RESULTS OF MODERN METHODS OF TREATMENT OF POLIOMYELITIS R W JOHNSON JR, J Bone & Joint Surg 27 223 (April) 1945

Johnson recommends in the acute stage bed rest, sedation for restlessness and pain and half-shell plaster molds or "Toronto" type splints for paralyzed, weakened or tender extremities in positions of relaxation Frequent checks are made of muscle power The presence of hyperesthesia or muscle tenderness is also checked

Except in cases of the encephalitic type, the author has not had clinical evidence of spasticity in the paralyzed extremities. Stiffness of the neck and back is usual in the early days, but this tends to disappear spontaneously. Radiant heat is administered intermittently as a stimulant to local circulation. In the convalescent period gentle massage is administered to the paralyzed or weakened groups and is increased slowly in depth and force as soon as hypersensitivity permits. Limited passive motion is begun in joints when muscle power is below 50 per cent, and active motion is started in an increasing range as the muscles grow in strength. Graduated exercises are given for weakened muscles. Patients who seem destined to have some disability are turned from invalidism and self pity toward an attitude of adaptability and compensation. In the wards the children help one another to achieve this end. Ward patients do much better in this respect than patients in private rooms. Later, underwater exercise in pools is used. The benefit of a crusade of the Sister Kenny type is that it makes physicians reexamine their own therapeutic procedures. Johnson has remained unimpressed by the claims of superiority of the Sister Kenny treatment. Patients are not cured, they recover, and the author does not rate recovery in case units, for misleading statistics are produced in this way. The proper unit is the weakened and paralyzed muscle, and recovery is judged on final muscle power as compared with the original degree of paralysis. The record of each muscle is kept separately. For this analysis the author has selected ten commonly paralyzed and important muscles: the gluteus maximus, gluteus medius, quadriceps, hamstring, gastrocnemius, tibialis anterior, deltoid, biceps humeri, triceps brachii and opponens pollicis muscles. Figures shown in tables concern 64 patients. The paralyzed muscle units reported include 350 in the lower extremity and 106 in the upper extremity. All muscles should have three months of careful and painstaking protection and treatment comparable to that given in cases of peripheral nerve lesions. At the end of such a three month regimen a prognosis of recovery can be arrived at, for the muscles can then be divided into three categories: (a) Muscles which have not recovered 30 per cent of power in three months. No return of useful power is to be expected, and these make up the permanently paralyzed extremities. (b) Muscles which by this time have 80 per cent or more power and can be counted on to function satisfactorily without further treatment except general supervision. (c) The group which has demonstrated some return of power and has a three month level of 30 to 75 per cent. These muscles have potentiality for further recovery to a point where useful function can be restored and are the important ones as far as further active treatment is concerned. No appreciable recovery continues beyond eighteen months even under ideal conditions, but untreated or inadequately treated muscles have been salvaged by this regimen as late as six to ten years after the acute attack, indicating a previous nerve recovery which had been masked or nullified by the overstretching or overfatigue of the muscle or by opposing contracture.

J A M A .

SUBARACHNOID ADMINISTRATION OF PYRIDOXINE HYDROCHLORIDE IN DISEASES OF THE NERVOUS SYSTEM. SIMON STONE, *J Nerv & Ment Dis* **100** 185 (Aug) 1944

Stone reviews the literature on the uses of pyridoxine in treatment of various diseases of the nervous system and reports its effect in a number of cases when introduced intrathecally. Pyridoxine hydrochloride in 30 to 50 mg doses mixed with 8 to 10 cc of spinal fluid was introduced into the lumbar sac of 26 patients, without any untoward results. Intrathecal administration is preferable to other methods because the solution can be placed in greater concentration and in closer contact with the affected nerve roots and involved areas in the spinal cord.

In almost all cases there was improvement in the feeling of well-being of the patients and in their behavior in the ward. Specific improvement was produced in the abnormal movements of Sydenham's chorea, in the rigidity of postencephalitic paralysis agitans, in the weakness and muscular tenderness of peripheral neuritis, in the weakness and contractures of anterior poliomyelitis, in the weak-

ness and paresthesias of infectious meningomyeloradiculitis and in the spasticity and hyperreflexia of multiple sclerosis

The beneficial results are probably due to the fact that diseased nerve tissue requires greater amounts of thiamine and pyridoxine for proper metabolic function

CHODOFF, Langley Field, Va

STUDIES OF FIBRIN FOAM AS A HEMOSTATIC AGENT IN NEUROSURGERY, WITH SPECIAL REFERENCE TO ITS COMPARISON WITH MUSCLE FRANC D INGRAM, ORVILLE T BAILEY and FRANK E NUISSEN, *J Neurosurg* 1 171 (May) 1944

A completely satisfactory hemostatic material for neurosurgical work should produce prompt control of bleeding, should give no (or very slight) tissue reaction and should not cause the formation of antibodies. The authors report the results of a number of experiments showing the superiority of fibrin foam and thrombin to other agents

The escape of a large amount of thrombin into the cerebrospinal fluid is not followed by any serious reactions. As compared with muscle thromboplastin, soaked fibrin foam appeared to have the following advantages: 1 It produces far less tissue reaction. 2 The supply is virtually unlimited. 3 An excess is innocuous. 4 It can be molded to conform to the contour of the bleeding surface. 5 If dislodged free in the ventricle, it can be absorbed. 6 Its use is superior in large bleeding channels, where a large plaque is required. 7 It is usable where muscle could seldom be used thus saving much time at operation.

There is a considerably greater tissue reaction to black silk and bone wax than to fibrin foam. Furthermore, fibrin foam is better than soluble cellulose in that (1) the foam structure holds the thrombin better than the fibrillar cellulose, (2) the fibrin foam is more readily cut into adaptable shapes and will better retain the contours of the bleeding surface, (3) it is more quickly and permanently adherent to the bleeding surface.

WHITLICK, Philadelphia

GROSS INTRACEREBRAL HEMATOMAS. REPORT OF 16 SURGICALLY TREATED CASES W B HAMBY, New York State *J Med* 45 866 (April 15) 1945

Hamby says that, while the commoner types of intracranial hemorrhage are well known, spontaneous, limited, removable intracerebral hematomas are less familiar. He reports 16 cases of gross intracerebral hematomas that were drained, with recovery in 14 cases and death in 2 cases. Cases of hemorrhage due to cranial injury with skull fracture have not been included in this series. One of the 2 deaths was due to massive pulmonary atelectasis and the other to a fatal recurrent hemorrhage from a ruptured aneurysm of a major cerebral vessel. In 7 cases the hematoma was associated with cerebral arterial disease and in 5 cases with intracerebral neoplasms (metastatic in 3 cases, meningioma in 1 case and astrocytoma in 1 case). In 1 case the hematoma was proved and in 3 cases it was suspected to be due to a ruptured aneurysm of major blood vessels. In 1 case there was delayed post-traumatic intracerebral hemorrhage.

J A M A

OSTEOMYELITIS OF THE SKULL. ITS TREATMENT WITH PENICILLIN AND REPAIR OF THE DEFECT WITH TANTALUM M T SCHNITKER and W D MCCARTNEY, *Surgery* 18 94, 1945

Schnitker and McCartney report 3 cases of acute spreading osteomyelitis of the frontal bone. They believe that penicillin has revolutionized the therapy of osteomyelitis of the skull of sinus origin. It overcomes the infection rapidly, limiting its spread and thus permitting early operation, with primary closure of the wound. The authors use a corneal incision and close the wound primarily without packing, instead of employing the classic inverted T incision and open packing of the wound, thus avoiding a deforming scar of the forehead. The

wound is irrigated with solutions of penicillin through a catheter left in the incision. It is felt that penicillin should be regarded as a bacteriostatic agent. It limits the spread of infection and permits early removal of the infecting nidus. In a few cases recovery occurred after use of penicillin alone, usually in the absence of sequestration.

The infection (nonhemolytic staphylococcus) in the first case reported was well controlled with penicillin but could not be eradicated with this drug. The infection was apparently cured on two occasions but recurred with cessation of treatment with penicillin, which had been administered in doses of 240,000 units daily. A rapid recovery was made after the entire skull anterior to the coronal suture was removed in one piece. A tantalum plate was used to repair the resulting defect in the frontal bone and was inserted seven months after the initial operation.

In the second case osteomyelitis of the frontal bone (aerobic nonhemolytic streptococcus and nonhemolytic *Staphylococcus albus*) had not responded to sulfonamide therapy and local operations on the sinus. Twelve days after the beginning of penicillin therapy (200,000 units daily) the infection was apparently controlled, and the entire osteomyelitic area was removed through a coronal incision in one piece. The defect was repaired with a tantalum plate, inserted six months later.

In the third case osteomyelitis of the frontal bone was controlled with prolonged penicillin therapy and external, radical excision of the frontal sinus. In this case there was evidence of a mass lesion involving the left frontal lobe. Repeated exploration of this area with the needle gave negative results, and it was concluded that edema of the brain underlying the osteomyelitis was the cause of the symptoms of cerebral abscess.

SHENKIN, Philadelphia

ADRENALCTOMY IN HYPERTRICHOSIS WITH MENTAL CHANGES R. GREENE, A. S. PATERSON and G. C. L. PILE, *Brit. M. J.* 1:698 (May 19) 1945

Greene and his associates report the case of a woman aged 25 who had hypertrichosis associated with mental changes, which gradually resolved after adrenalectomy. The psychologic changes preceded the external physical changes. When first seen, she was drifting into a tense hypochondriacal state. The removal of most of the causes of her anxiety did not bring about her recovery. Only after operation was she set on the road to recovery.

J. A. M. A.

INTRAORAL SPLINT FOR FACIAL PALSY A. G. ALLEN and D. W. C. NORTHFIELD, *Lancet* 2:172 (Aug. 5) 1944

Allen and Northfield describe a new form of splint to prevent stretching of paralyzed facial muscles by antagonists and gravity. This device is an intraoral plastic hook for the corner of the mouth. It is anchored to an artificial plate if the patient is edentulous or against the natural teeth. Each splint is fitted to the individual patient by previously obtaining a plaster impression of the corner of the mouth. The advantages of this splint lie in its lack of irritation, its inconspicuousness and its stability when in place.

McCARTER, Boston

# Society Transactions

## CHICAGO NEUROLOGICAL SOCIETY

Ben W Lichtenstein, M D, *President, in the Chair*

*Regular Meeting, Oct 9, 1945*

### Neurinoma of the Twelfth Nerve DR ERNST HAASE

Neurinoma of the twelfth nerve is a rare tumor I found reports of only 4 cases, 2 of extracranial and 2 of intracranial tumors Friedman and Eisenberg (*Ann Surg* 101 834, 1935) and Capella (*Rev di chir* 2 169, 1936) successfully removed neurinomas of the hypoglossal nerve in its extracranial course Capella's case was one of generalized familial neurofibromatosis De Martel (1933) operated on a tumor in the intracranial course of the hypoglossal nerve, the growth being attached to the canalis hypoglossi Bailey, Buchanan and Bucy reported the case of a typical neurinoma of the right hypoglossal nerve deeply indenting the bulb, in addition, there were neurofibromatous involvement of many peripheral and sympathetic nerves and of the extracranial portions of the ninth to the twelfth nerve, spongioblastoma of the optic chiasm, astrocytoma of the cerebellum and gliomatous nodules in the cerebral and cerebellar cortex

In my first case the tumor was not correctly diagnosed because the clinical picture was confusing, showing, in addition to atrophy of the left half of the tongue with fibrillation, Argyll Robertson pupils and involvement of the left trigeminal, facial and acoustic nerves and the right accessory nerve, as well as spastic paresis and sensory disturbance of the right side of the body and diminished appreciation of pain and temperature on the left side between the second cervical and the eleventh thoracic nerve Necropsy showed a neurinoma of the left hypoglossal nerve almost completely filling the foramen magnum invading the occipital bone and extending laterally to the internal acoustic meatus Unfortunately, the spinal cord was not examined

In the second case, in which the correct diagnosis was made and operation performed by Dr Bucy, a roentgenogram of the base of the skull revealed erosion of the occipital bone around the left canalis hypoglossi The patient had complained of a tickling sensation in the throat, coughing and choking on swallowing, dizziness and pains in the left suboccipital region The left half of the tongue was atrophic and fibrillating, the left glossopharyngeal and accessory nerves were slightly involved Two tumors of the intracranial portion of the left hypoglossal nerve were removed and found to be neurinomas

### DISCUSSION

DR GEORGE B HASSIN Some features of Dr Haase's cases pertain to involvement of the ninth, tenth, eleventh and twelfth cranial nerves, especially in the second case, in the first case the involvement was less extensive Combined extracranial involvement of the aforementioned nerves, of all or of several of them only, always indicates, in my opinion, a surgical condition in the form of a foreign body or a tumor Such a lesion may be suspected and located even before roentgenographic examination has been made I know of a case in which the last four cranial nerves were affected by a calcified lymph node of the neck at the jugular foramen Nothing could be palpated or visualized, and only the history and the clinical picture of the syndrome of the jugular foramen, that is, involvement of the ninth, tenth, eleventh and twelfth nerves, suggested pressure by a lymph node This diagnosis was borne out by roentgenographic examination

and subsequent operation. A number of contributions have appeared in which the cause of the syndrome of the jugular foramen was a bullet, but few in which the cause was a tumor, as recorded by Dr Haase. The lesion may not be demonstrable, but, as has been stated, it may be suspected on the basis of the combined involvement of some of the four last cranial nerves.

There are certain features in the first case of Dr Haase which I cannot understand. The Argyll Robertson pupil and other signs of involvement of the central nervous system certainly had nothing to do with the implication of the cranial nerves unless there was pressure on the medulla. Dr Haase may be able to explain them.

DR ERNST HAASE. I do not think I can explain these symptoms. Had the spinal cord been examined, an explanation might have been found.

### Cerebral Thromboangitis Obliterans DR GEORGE PERRET

Of a series of 9 verified cases of cerebral thromboangitis obliterans, 1 in which the diagnosis had been made clinically was presented and discussed. A woman aged 42, of Irish descent, had had transient headaches, attacks of diplopia and difficulty in reading for four years, the symptoms following a slight infection of the upper respiratory tract. Later she had bilateral defects of the visual fields, more severe attacks of diplopia, transient paresthesias on the left side and an episode of aphasia, still later, she had repeated attacks of paresthesias and progressive speech and reading difficulties. When hospitalized in March 1945, she had right homonymous hemianopsia, hesitancy of speech, complete alexia, being able only to spell out words, increased deep reflexes on the right side, and changes of personality. Except for a mottled appearance of the extremities she had no other peripheral vascular disturbances. Roentgenographic studies of the skull, spinal puncture and electroencephalographic examination revealed no abnormalities, the blood pressure was 150 mm of mercury systolic and 90 mm diastolic. Ventriculographic studies showed dilated ventricles and enlarged subarachnoid spaces, and a diagnosis of cerebral thromboangitis obliterans was made. This was verified at operation. An osteoplastic craniotomy on the left side exposed a thickened and opaque arachnoid with large subarachnoid spaces and numerous small, white, stringlike vessels, which were completely obliterated, distributed over the frontal and parietal lobes. The underlying gyri were yellow and atrophied. An obliterated artery was removed for microscopic study.

The vessels were completely occluded with proliferated endothelial and subendothelial connective tissue, and only a few small recanalized channels were present. There was no sign of fresh inflammatory reaction, and the internal elastic membrane was intact. The lesion was confined to the inner layer of the vessel. The surrounding arachnoid was fibrotic as a result of earlier perivascular infiltration. The obliterated vessels were small arteries, scattered over the entire cortex. They were much smaller and more elastic than arteriosclerotic vessels and failed to show the characteristics of periarteritis nodosa. The disturbance of blood supply to the various cortical areas affected resulted in cortical necrosis and atrophy. The transient symptoms favor the hypothesis that angiospasm is the etiologic factor in producing the changes in the endothelial cells. No known therapy has been reported for this type of thromboangitis obliterans. Spatz, Lundenberg, Foerster, Scheinker and others have reported similar cases in which the condition was recognized at autopsy.

### DISCUSSION

DR L. I. POITLOCK. It is useful to present cases of a type which afford so much difficulty in diagnosis. I am grateful to Dr Perret for reporting the existence of cerebral thromboangitis.

DR VICTOR E. GONDA. I wonder whether an arteriographic examination would help in the diagnosis, I should like to ask whether this was tried and, if so, whether it was successful.



DR RICHARD B. RICHTER I wish to ask Dr Perret whether he believes that the vascular lesions in cases of cerebral thromboangitis obliterans are similar etiologically to those of the peripheral type and whether he thinks that the vascular lesions, in some cases at least, may not be the consequence of an infectious or a toxic-infectious process. It is perhaps significant that the symptoms in Dr Perret's first case began after an infection of the upper respiratory tract. The infectious or toxic origin of this type of vasculitis might well be diverse, rather than specific. For example, several years ago I described the case of a boy 14 who died four months after a typical attack of poliomyelitis, which occurred during an epidemic of the disease. Pathologically, in addition to inflammatory reactions and neuronal destruction in the spinal cord and brain stem, which were consistent with a diagnosis of poliomyelitis, there were widespread productive changes in the walls of the smaller arteries of the brain and cord. These were chiefly in the intima of the vessels and were sufficiently great to occlude some of them and so lead to foci of softening.

DR R. P. MACKAY What percentage of the 9 patients reported were women? It is known that peripheral thromboangitis is rare among women.

DR BEN W. LICHTENSTEIN I enjoyed Dr Perret's presentation, but I wish to point out that verification of the diagnosis of cerebral thromboangitis obliterans is a problem for the histopathologist. The microscopic sections shown on the screen do not reveal any evidence of angitis, that is, inflammation within the component portions of the blood vessel. The lesion presented may have been healed, but the fact that the tunica elastica appears intact makes it improbable that any severe inflammation was present at any time. The thrombosis may have been the result of any one of many other disorders.

DR GEORGE PERRET In answer to Dr Gonda, Sargo has published reports of cases in which cerebral arteriographic examination gave evidence of obstruction of vessels.

In reply to Dr Richter. In some of the cases symptoms followed a history of infection, in others they did not. One woman gave a history of falling while skiing, and shortly thereafter paresthesias developed, which were not related to the site of her injury. It is possible that infectious processes may be an etiologic factor in thromboangitis obliterans. Spatz also reported cases in which vascular symptoms developed after infectious diseases, but at no time could he prove the presence of organisms or of other manifestations of infection in the vessels or the perivascular tissues. He expressed the belief that cerebral thromboangitis obliterans was a primary process which occurred in the cerebral vessels and produced the same changes as those in the peripheral vessels of the extremities.

In the present series 4 of the patients were women and 5 were men. My colleagues and I have also seen cases of peripheral thromboangitis obliterans in women. We have been able to help patients with this condition by performing lumbar sympathectomies. This operation is helpful in the peripheral type of this disease. I do not know whether cervical sympathectomy, as suggested by Foerster, would help the cerebral type.

The slides were studied by competent pathologists, and all agreed as to the presence of proliferated endothelial and subendothelial connective tissue which completely obliterated the lumen of the vessels, as is characteristic of thromboangitis obliterans. I refer Dr Lichtenstein to the beautiful photomicrographs published by Spatz and Lindenberg, which are similar to those I showed tonight. I am sorry I do not have any slides illustrating the early pathologic changes in the vessels, it was found better for the patient to remove for study only completely obliterated vessels.

#### Contractures Following Experimentally Produced Lesions of the Peripheral Nerves DR IRVING C. SHERMAN

This report deals with the development and treatment of contractures in the muscles of the cat's leg following experimentally produced lesions of the sciatic

nerve without the complication of any contiguous injury. In general, three types of lesions of the sciatic nerve were available: (a) denervation, (b) primary suture, and (c) delayed suture, i. e., secondary operation performed sixty days after the original section, with suture of the nerve. The following therapeutic regimens were carried out: (a) no treatment, (b) massage and passive motion for five minutes daily, (c) massage, passive motion and electrotherapy for five minutes daily, and (d) massage, passive motion and electrotherapy for fifteen minutes daily. All treatment was given under the constant supervision of an approved physical therapist.

Contractures developed in the denervated muscles in 100 per cent of cases if they were maintained in a shortened position for from forty-five to one hundred and five days. Treatment did not influence this. After section of the sciatic nerve and suture, without immobilization, contractures developed frequently in one or more muscles below the knee. Ninety days after primary suture the incidence of contractures was 84.2 per cent, after delayed suture it was 100 per cent. Contractures were most frequent in the dorsiflexors of the foot because of the spontaneous maintenance of a shortened position when the animal rested. Contracture in one group of muscles tended to prevent it in opposing muscles.

In untreated animals contractures of the dorsiflexors of the foot were less frequent, less severe and less persistent after primary suture than after secondary suture, with the former the peak frequency was 47.1 per cent after ninety days, and with the latter, 72.7 per cent after forty-five days. Massage and passive motion definitely decreased the frequency and severity of contractures after primary suture, the peak frequency being 21.7 per cent after sixty days. After delayed suture, similar treatment seemed to delay development of the peak frequency at forty-five days and undoubtedly decreased the severity of the contractures.

Addition of electrotherapy to massage and, passive motion delayed the appearance of contractures in animals with primary sutures, however, after sixty days it seemed to nullify the influence of massage and passive motion. The longer the period of electrotherapy, the more closely the frequency and severity of contractures approximated those for untreated animals, in general, electrotherapy for animals with delayed suture had no beneficial influence. Furthermore, it favored development of contractures in the unparalyzed antagonists of paralyzed muscles.

Spontaneous movement after recovery of function was as good as, or better than, any form of artificial treatment. After delayed suture residual contractures were similar in frequency and severity in treated and in untreated animals. Contractures were more frequent if the extremity was immobilized than if it was permitted to be free.

#### DISCUSSION

DR VICTOR E. GONDA: Would Dr. Sherman tell us what type of electrical treatment was used? Had the status of degeneration been determined by testing with electricity for reaction of degeneration?

DR PERCIVAL BAILEY: Does Dr. Sherman have any explanation of the increased contracture after electric therapy?

DR L. J. POLLOCK: May I presume to answer the last question, which is concerned with electrodiagnosis? Dr. Sherman's report is part of a study which my colleagues and I have made on experimentally produced lesions of peripheral nerves in cats. This investigation included studies of motion, sensation, atrophy and fibrillation, as well as the orthodox methods of electrodiagnosis. From this there has developed an accurate method of study in kinetics of stimulation of muscles. It follows, therefore, that we have ample data on reaction of degeneration. There is no correlation between contracture and the kinetics of stimulation. We do not have any data which would explain the incidence of a greater number of contractures in electrically treated animals. We have observed that spontaneous fibrillation continues for a longer period in animals so treated.

DR GEORGE PERKIT: I should like to ask whether there is any relation between the contracted muscles and the ankylosis of the joints.

DR IRVING C SHERMAN In reply to Dr Perret's question Each animal was carefully examined after death The tendons about the joint were divided, and if complete mobility of the joint could not be obtained the animal was discarded Furthermore, the joints were examined for gross pathologic changes

I cannot answer Dr Bailey's question as to the effect of electrotherapy on the frequency and severity of contracture It may be clarified by histologic studies

Dr Gonda asked what type of electrical treatment was employed A 60 cycle alternating current was used A mechanical appliance was set up so that the stimuli were delivered at regular intervals, in order to produce a good contraction of the muscle In the group treated for five minutes daily 12 stimuli were given per minute, in the animals treated for fifteen minutes 40 submaximal tetanic contractions were produced each minute, to conform to the type of treatment given by Guttman and his group

### The Brain After Intermittent Exposure to Simulated High Altitude

DR ARTHUR V JENSEN and DR WILLIAM F WINDLE

The present study was undertaken to determine possible effects on nerve cells of exposure to tolerably low partial pressures of oxygen intermittently over relatively long periods Young adult male guinea pigs were subjected to a simulated altitude of 23,000 feet (7,600 meters) six hours a day for six days a week until they had accumulated totals of one hundred, two hundred, three hundred and five hundred hours in a decompression chamber At appropriate periods experimental animals and controls were killed This was done, with the animal under pentobarbital anesthesia, by perfusion through the vascular system of a dilute concentration of solution of formaldehyde U S P, in order to obtain fixation of the nervous system and other organs in situ The brain was removed and placed in fixing fluid for several days It was sectioned serially and every tenth section was stained with an improved buffered thionine technic at a pH of approximately 4.5 In some experiments the Weil method for myelin sheaths was employed

Animals gained weight throughout the period of the experiment and exhibited no symptoms of cerebral damage Acclimatization took place, the number of red corpuscles and the hemoglobin value of the blood increasing significantly after two hundred hours

Careful comparison of sections through the brains of experimental animals and of the controls revealed no hemorrhages, vascular changes or glial proliferation No cytologic alterations in nerve cells could be seen No reduction in the number of nerve cells could be detected by inspection No changes in the myelin sheaths of nerve fibers and no abnormalities in the fiber tracts of the brain were observed

Further experiments are in progress to study possible effects of exposure to even lower partial pressures of oxygen, and one of these has been completed Guinea pigs intermittently subjected to an altitude pressure simulating 23,000 feet for one hundred hours and then to an altitude of 30,000 feet (10,000 meters) for another one hundred hours showed no overt symptoms of injury to the brain, although 1 animal exhibited transient vestibular signs Four of the animals were studied histologically Each had focal areas of necrosis in the cerebellum No generalized cytopathologic change was exhibited

### DISCUSSION

DR WILLIAM F WINDLE We fully expected to see pathologic changes in animals exposed to an altitude of 23,000 feet Dr Becker and I had studied the effect of asphyxia in the newborn and had clearly demonstrated not only marked cytopathologic changes, but also gross lesions, correlated with changes in behavior and in learning ability That was the background with which Dr Jensen and I entered this study We have not put our altitude animals to psychologic tests, although we plan to do so We observed no overt changes in behavior even after exposure to an altitude of 30,000 feet, with the sole exception of the animal that rolled onto its side The animals were apparently normal Histopathologic

changes, we are convinced, are not present. We could find nothing with the fairly well controlled methods. We do not hold that there are not some, perhaps chemical, changes.

I do not doubt there is some impairment while the animals are at altitude, but when they are down one cannot see anything. Of course this study concerned guinea pigs. We are aware of the observations of the air corps, they are dealing with men. We were surprised not to observe hemorrhages and other changes, but we are reporting what we found at 23,000 feet—that is—nothing.

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Ben Lichtenstein, M D, *President, in the Chair*

*Regular Meeting, Nov 13, 1945*

**Cerebral Schistosomiasis** Report of a Case DR I JOSHUA SPEIGEL

**Acute Myelitis** Clinicopathologic Study of a Case DR GEORGE B HASSIN  
and DR SAMUEL B BRODER

A frequent cause of acute paraplegia may be acute myelitis, as is evident in the case reported here. A white man, aged 46, complained of weakness in the legs following an acute infection of the upper respiratory tract. Since the neurologic examination revealed no abnormality, his condition was thought to be functional, and after hypnosis and galvanic stimulation he was able to return to work. Six weeks later there suddenly developed paraplegia and urinary and fecal incontinence, as well as a sharp sensory level for all modalities at the eighth dorsal dermatome and hyperthermia (105 F). Repeated spinal punctures revealed leukocyte counts varying from 10,700 to 28,000 cells, a positive Pandy reaction and normal dynamics. Since penicillin and sulfonamide drugs failed to lower his temperature permanently and since an epidural abscess was suspected, a laminectomy was performed, with negative results. The patient died on the forty-second postoperative day.

Histopathologic observations revealed dense infiltrations of some blood vessels in the gray and especially in the white substance of the spinal cord with lymphocytes and plasma cells, and of other vessels with compound fat granule corpuscles, there were scattered areas of softening and necrosis, with vast disruption of the white substance in areas which were especially involved, such as the thoracic. The nerve cells of the gray matter remained unaffected, while the meninges were for the most part infiltrated with lymphocytes. The subarachnoid space and some spinal roots, especially at the level of the softened segments of the spinal cord, were packed with compound fat granule bodies. The changes were comparatively mild in the cervical and sacral segments of the spinal cord, and in the medulla, brain stem and cortex they were mostly proliferative (productive), in the form of newly formed capillaries.

Of the changes described, the inflammatory ones (myelitis) were primary, and on them were superimposed those of softening and necrosis, which were either the sequels of toxemia or the manifestation of an anaphylactic reaction of the spinal cord to an infection (evidently respiratory).

**Return of Sensation After Denervation and Regeneration of Sutured Nerves** DR ELI L TIGAY, DR MAURICE A SCHILLER and DR IRVING C SHERMAN

Immediately after severance of the nerve there is a loss of touch sense and, to a less degree, of temperature sense over the area of anatomic sensory supply. Within this area is a narrow intermediate zone, adjacent to the border in which pinprick and extremes of temperature are felt. The remaining central zone is completely insensitive. Head and his group expressed the belief that this pattern

of sensory change is due to morphologically different systems in the afferent pathway—one serving epicritic and the other protopathic sensation. Preservation of pain sensation in the intermediate zone of about 1 cm width is due to dual innervation from adjacent nerves, as shown by Woolard, Waddell and Harpman. For a period after nerve section, the recovery of pain sense within certain areas of the anatomic supply may occur as a result of overlap, as described by Pollock. He found that this sensation returned by shrinkage of the analgesic area as time progressed. Later, Weddell, Gutmann and Guttman demonstrated that this shrinkage is due to the ingrowth of nerve fibers from surrounding normal nerves. Thus it is seen that the early return of pain sense within the anatomic border of the severed nerve is not due, as proposed by Head, to an accelerated regeneration of protopathic fibers but is the result of an ingrowth of uninjured adjacent nerves.

That area of skin which remains analgesic, however long the period which has elapsed after denervation, was designated the isolated supply of the nerve. Sensation returning within this area could occur only as a result of regeneration of the injured nerve.

In denervations of the sciatic nerve in cats the recovery of pain sensation as a result of overlap can be demonstrated. This occurs within the borders of the anatomic sensory supply when no regeneration is possible. As in man, so in the cat—recovery of sensation resulting from regeneration is often characterized by relatively large areas of skin becoming imperfectly sensitive, in contrast to the shrinkage of areas of analgesia resulting from nerve overlap.

A suture delayed for sixty days after section results in delay in beginning of recovery of sensation, incompleteness of recovery or, in some cases, failure of recovery.

#### One Component of the Extrapyrarnidal System DR W S McCULLOCH, DR RUTH RHINES and DR H W MAGOUN

By strychninizing the cortex and recording the electrical activity of the brain stem of the monkey, a pathway has been found to arise from area 4-S and diverge from the corticospinal tract in the pons to reach the bulbar reticular formation. Electrical stimulation of the bulbar reticular formation in the cat and monkey has been found to exert a general inhibitory influence on motor activity, whether induced reflexly from the brain stem in an animal with decerebrate rigidity or from the motor cortex. This influence appears to be mediated by reticulospinal connections descending in the anterior portion of the spinal cord. As is evident from its physiologic properties, this corticobulboreticular and reticulospinal pathway is an extrapyramidal system mediating relaxation.

#### DISCUSSION

DR PERCIVAL BAILEY: I wonder whether the society realizes the importance of this contribution. It is the first time an extrapyramidal system has been pinned down, classified and defined.

#### PHILADELPHIA PSYCHIATRIC SOCIETY

O Spurgeon English, M D, *Presiding*

*Regular Meeting, Oct 12, 1945*

#### Evaluation of Results of Electric Shock Treatment of the Psychoneuroses DR MARTIN H ROBINSON

This study was carried out in an attempt to determine whether electroconvulsive therapy has any place in the treatment of the psychoneuroses. Sixty-six cases were included: 19 cases of reactive depression, 34 cases of anxiety state, 5 cases of conversion hysteria, 6 cases of obsessive-compulsive neurosis and 2 cases of hypochondriasis. Remissions occurred in 21 per cent of all cases. This number included cases of reactive depressions and anxiety states. Improvement was

observed in 54 per cent of the total number of cases. The precipitating factors included marital discord, sexual problems and disruption of the home.

Conversion hysterias and hypochondriases were least benefited.

Obsessive-compulsive states showed some significant improvement, and it is felt that a longer series of electric shock treatments is required in cases of this disturbance. The most frequent symptoms noted in the series were depression, anxiety, somatic pains, insomnia and lack of interest. Electroconvulsive therapy was most helpful in removing affective distress. It also made the patient more accessible to psychotherapeutic efforts.

The treatment of psychoneuroses has no specific measures or any short cuts. The symptoms are often incapacitating and long drawn out. Electroconvulsive therapy is worthy of consideration in that it removes many of the affective disabilities, shortens the period of disablement and makes the patient more amenable and accessible to psychotherapeutic efforts.

#### DISCUSSION

DR J. C. YASKIN: This is an important paper, considering that most extramural psychiatric patients are psychoneurotic. Any aid one can obtain in shortening the period of psychotherapy is very useful. Dr. Robinson's presentation is factual. At least, his results correspond with those obtained in patients who have come under my own observation. A few comments may be pertinent. I believe that electric shock therapy will relieve depression, certain types of anxiety and certain tension situations and that there will be an improvement in the sleep cycle. I do not believe that electric shock therapy will influence one iota the fundamental disorder of the psychoneurosis, the compulsive-obsessive neurosis or the anxiety hysterias, which constitute 65 per cent of all psychoneuroses. I believe that in the treatment of patients who have become extremely depressed and suicidal one has the choice of prolonged narcosis, prolonged hospitalization and shock therapy. Dr. Robinson has already said that electric shock therapy does not take the place of psychotherapy with these patients.

I am not altogether in agreement with Dr. Robinson regarding the large percentage of patients with reactive depressions. It is hard for me to conceive that 19 of some 60 patients had reactive depressions. In my experience, most psychoneurotic patients have proved rather to have manic-depressive psychosis, and they have been amenable to electroconvulsive treatment. Some have proved to be schizophrenic. I do not believe that many patients with an obsessive-compulsive state are benefited, but I should like to caution that many patients with so-called obsessive-compulsive psychoneurosis have actually a manic-depressive psychosis, depressed type, with compulsive trends. If a person has no symptoms up to the age of 35 and there then develops a depression with compulsive trends, this is not an obsessive-compulsive neurosis. Such patients will receive considerable benefit from shock therapy.

Lastly, I should like to emphasize that electric shock therapy should not be used with psychoneurotic patients amenable to other forms of psychotherapy. If the patient can keep her job or do her housework, it is better to resort to psychotherapy than to take a short cut, which is not a permanent cure.

DR HERBERT FREED: I agree with Dr. Yaskin that this procedure should be an aid to treatment and not the essence of therapy. If the patient can work or make a social adjustment, he should not be institutionalized. Patients cannot be given psychotherapy while they are in the midst of a depression or while caught in the throes of anxiety.

It has been my experience that in certain cases shock therapy will remove a sufficient quantity of depression or anxiety to make a therapeutic interview feasible. Kalinowsky claimed that he did not obtain good results in patients with anxiety neuroses. Dr. Robinson reports that the results were satisfactory in a fairly high percentage of patients. I, too, have had some good results in a smaller series.

I should emphasize again that the foundation for permanent results in treatment of these entities lies in giving the patient insight into the basis of his anxiety, such as repressed hostility or aggression, an insight which can come only with psychotherapy

DR CHARLES I OLIER The impression I have gained from my rather limited experience with psychoneurotic patients treated with electric shock is that they have not been much benefited by it. The usual story, particularly with psychasthenic persons, is that after a little they are right back where they started. I wonder whether the mere fact that the psychoneurotic patient is hospitalized for four or five weeks—that he is away from home, family and usual responsibilities, does not of itself contribute to the improvement that is seen. Along the same lines, I wonder whether electric shock therapy applied on an ambulatory basis to such patients would not give similarly favorable results.

DR S DEWITT LUDLUM I hesitate to say what I think about it. It would take too long. It seems to me that the reality could be better understood in the light of experiments reported by Gellhorn. He thinks that shock treatment works on the autonomic nervous system. He trained rats to conditioned reflexes. When he gave them electric shock treatments, they lost their newly conditioned reflexes and reverted to their normal reflexes. In the case of the patient with a mental disease, his symptoms represent a new conditioning. If something can be done to blot this out, he will revert to his original conditioning. A change is produced in the blood proteins, in the blood pressure and the temperature and in the mental symptoms. It occurs in rats, and it occurs in people. There is a physiologic basis, and when through electric shock therapy the patient is made to revert to his original conditioning he has normal thinking. These physiologic symptoms of conditioning provide a method of measuring the number of shocks necessary to return the patient to his normal physiologic state.

DR LESLIE R. ANGUS, Hartford, Conn. Two questions come to mind. The first concerns the way in which the psychotherapy was used. Was an attempt made to give it in the immediate postshock state, when the patient was more receptive to therapy, or was it carried out consistently over the period between the shock treatments?

The second question is a practical one, based on the fact that some of the patients coming for psychiatric treatment have read articles in the newspapers and magazines and demand shock therapy. In cases in which there is doubt as to the advisability of the treatment, one of the factors in arriving at a decision is whether the treatment, if used, would do harm. In the present series, were there any adverse effects from carrying out the shock therapy over a long period? Dr. Robinson did not mention any, even when patients had received over twenty treatments. Did any spontaneous convulsions follow the shock treatment?

LIEUT. ROBERT KIMMICK, MC, AUS. I have little to add except that the situation is somewhat different at the Army general hospital with which I am associated. We have selected pretty carefully only psychotic patients. A few psychoneurotic patients have come under treatment, with only fairly satisfactory results. It is mainly the depression and agitation of the patients that seem relieved. The more basic patterns remain. The few patients treated with only partial improvement had reactive depressions. The reactive depressions, as a rule, have cleared up rather quickly without shock therapy because of the causative factors in the Army setup.

DR MARTIN H. ROBINSON. I want to thank all the discussants for their interesting and valuable comments. I agree that this treatment is most effective in patients showing pronounced affective disorders. I believe that electric shock treatment will lift them out of that state and put them in a frame of mind in which psychotherapy can do something for them. Dr. Yaskin raised the question whether the percentage of cases of reactive depressions was not rather high. At times it is difficult to differentiate between reactive depression and manic-

depressive psychosis, depressed type I am beginning to feel that it does not matter which of the two labels is applied

With respect to the obsessive-compulsive neuroses, the series presented was rather short, but from my experience there does not seem to be any very effective treatment for this disorder. Psychoanalysis, perhaps, would offer some hope. Psychoanalysts themselves are cautious in their predictions. Another measure being used is prefrontal lobotomy, but I think electric shock should be tried before anything so drastic as that is carried out.

Dr. Freed, in a sense, agrees that the treatment is valuable in the acute emergency, when the patient becomes a problem at home, if electric shock therapy can abort the attack and make the patient more accessible to psychotherapy, it is worth a trial.

Dr. Oller raised an interesting point as to whether hospital care in itself might be just as beneficial as shock therapy. I did not carry out any control study on this point. Therefore I cannot give any definite answer.

Dr. Ludlum's observations are valuable. They bring up the old controversy. Is the psychoneurosis on a functional or an organic basis? I believe I mentioned the theory of Moriarty and Weil that electric shock has an organic effect on the hypothalamus.

With regard to Dr. Angus' question as to when psychotherapy is effective. The purpose is to gain rapport with the patient and attempt some transference. Obviously, it would be impossible to get good results from psychotherapy when a patient is in a nervous state. From that standpoint, I believe that in cases of severe affective disturbances one can gain rapport with the patient and obtain some transference with removal of the disturbed affective component. After the first treatment, psychotherapy can be tried. No pathologic changes due to electric shock were observed. Kalinowsky stated that patients with obsessive-compulsive states should have twenty shock treatments. Some cases have been reported in which forty to sixty electric shock treatments were given without any obvious damage. The amount of postmortem material on patients who have had electric shock is very meager.

#### Reevaluation of Contraindications to Electric Shock Therapy Dr. MATTHEW T. MOORE

The early enthusiastic application of convulsive shock treatment of mental illnesses, owing perhaps to indiscriminate and incautious use, resulted in numerous complications and occasional deaths. These unlooked-for, untoward effects led to a swing in the direction of conservatism, with resultant denial of treatment to many patients who would have benefited from this procedure. The severe convulsive reactions encountered with metrazol shock therapy and the early inexperience with methods of overcoming or subduing complications evidently produced the timidity with respect to contraindications which carried over to electric shock therapy.

A sufficiently large body of literature and experience has accumulated to provide a basis for reevaluating the indications and contraindications which, until recently, have been considered an unquestioned barrier to convulsive shock treatment, namely, acute infections and febrile diseases, advanced disease of the heart and kidneys, advanced age, bone atrophy in long-bedridden patients, pronounced spinal curvature and osteoarthritis, severe thyrotoxicosis, malignant growths, thrombophlebitis, advanced general arteriosclerosis, organic disturbances of the central nervous system and tuberculosis.

Some of these contraindications can now, in the light of experience and judgment, be eliminated from this category and greater freedom of use of this treatment be permitted. This applies to cardiovascular diseases with and without hypertension, advanced age; latent, arrested or even active tuberculosis, some cases of generalized arteriosclerosis in which a differential diagnosis between cerebral vascular involvement and involutional psychosis has not been established, organic



disease of the central nervous system, such as dementia paralytica, spinal curvatures, and osteoarthritis

Six representative cases were reported. Such conditions as cardiovascular disease, with and without hypertension, pulmonary fibrosis secondary to tuberculosis, spinal curvature, and generalized arteriosclerosis were represented. No complications arose secondary to electric shock treatment, and in the main the results from the psychiatric standpoint were gratifying.

#### DISCUSSION

DR BENJAMIN GOULEY. All can agree with Dr Moore that in the earlier years of electric shock treatment many fears with regard to making worse serious organic disease did not have a basis in fact. One of the great fears in instituting treatment of this kind was that concerned with what such treatment might do to organic heart disease. Certainly, there has been little aggravation of preexisting heart disease with such treatment. Dr Moore's paper has been matched by others, in which patients with various types of heart disease were not considered bad risks for shock treatment. I think that almost every patient of the Philadelphia Psychiatric Hospital has undergone electrocardiographic examination before treatment. After going over about 1,500 tracings, I can recall few instances in which organic heart disease, revealed by electrocardiographic examination, was made worse. I am under the impression that there has been 1 death as a result of shock treatment. Unfortunately, in that case electrocardiographic studies were not made. There arises the question whether the death was due to the electric shock treatment.

I am under the impression that the incidence of heart disease in the mentally sick has been exaggerated. I do not believe that there is as much heart disease in this psychiatric hospital as in a general hospital, and I doubt whether the shock therapist has to worry as much about the effects of his treatment as the surgeon does about such matters as anesthetics. There are, however, certain types of heart disease that might be looked on askance and shock therapy employed with reluctance. Certainly, I should not want to treat any one with acute or subacute myocardial infarction. Few such patients will enter an institution for the mentally ill. I have seen good internists much surprised when a patient of that type died and autopsy showed only myocardial infarction. Healed infarctions offer no barrier to treatment. A healed infarction in the anterior wall of the heart is more serious with respect to the risk of sudden death than is involvement of the posterior wall. In the presence of bundle branch block, especially what is called the left bundle branch variety, one has a sign that suggests conservatism in treatment. A patient with right bundle branch block is not a bad risk, no matter how loud the murmur he has nor how bad the electrocardiographic tracings may be. However, there are not enough such patients to warrant carelessness. One has to speak in terms of hundreds of cases before one can come to a satisfactory conclusion with regard to the more serious types of heart disease. A little caution will hurt neither the physician nor the patient.

DR J C YASKIN. I feel that patients should not receive this treatment without first having an electrocardiographic examination. The medicolegal phase should not be disregarded. No treatment should be carried out without thorough physical, electrocardiographic and minimum laboratory studies.

DR HERBERT H. HERSKOVITZ. About three years ago the society held a symposium on electric shock, and all of us listed the complications we had experienced, but we were generally agreed that patients with tuberculosis, cardiovascular disease, particularly arteriosclerosis, and bone deformities should not be treated. Since that time my associates and I at the Norristown State Hospital have not deviated much from those decisions. We have taken a chance with a few patients with moderate hypertension, but if cerebral arteriosclerosis is present, as found on examination of the eyegrounds, we will not give the patient electric shock. We do not worry about bone deformities because we use curare. We will take no

chances with tuberculosis, whether the lesion is healed or active. Although Dr Moore presented 1 case of tuberculosis, the disease was not active. I know of a few cases in which healed lesions were transformed through electroshock into "galloping consumption."

DR. N. W. WINKELMAN. My colleagues and I are now in the midst of treating a young woman physician who received pneumothorax and electroconvulsive therapy simultaneously and is now receiving pneumothorax and insulin shock treatment. Apparently, there has been no change in her pulmonary condition. We are continuing treatment, and she is apparently thriving on it. Whether or not tuberculosis will prove to be an absolute contraindication is not as yet definitely determined.

DR. I. RODRIGUEZ, Washington, D. C. I treated a patient with moderately advanced congestive heart failure who was suicidal, it was a question of treating him with electric shock and taking a chance of killing him or letting him do away with himself. The family understood this, and nothing happened to him after the conventional administration of treatment. He was appreciably better. I have had occasion to treat several patients with auricular fibrillation and advanced myocardial degeneration as determined by routine electrocardiograms. Nothing happened. I do not now make electrocardiographic examinations as a routine.

DR. MATTHEW T. MOORE. I wish to thank the discussers especially, for they have brought up a number of points which, for lack of time, I did not present this evening. My intent was not to invite you to throw caution to the winds, on the contrary, this sample group of cases was reported to show that the former arbitrary and rigid contraindications could and should be relaxed, so that many patients could be receiving necessary treatment. Dr. Gouley mentioned the possible complications in treating patients with rheumatic heart disease. Only 1 case has thus far been reported in the literature in which an old endocarditis flared up after convulsive shock therapy. This case was reported by Ziegler, who stated that the condition subsided and the patient's mental state improved. Several patients with long-standing rheumatic heart disease have been treated without complications. Persons with advanced myocardial degeneration and decompensation obviously should not receive shock treatment. A review of the literature shows that many institutions are using convulsive shock therapy for patients with suicidal intent despite the presence of a serious cardiac condition. Kline and Fetterman, and Evans have treated a series of patients who had severe cardiovascular disease. Not only did these patients withstand shock treatment, but the psychiatric results were good.

I am fully in accord with Dr. Yaskin with regard to caution. My colleagues and I agreed that each patient should be studied carefully and individualized as regards the indications for treatment in the light of his physical state and the likelihood of his recovery.

With respect to Dr. Herskovitz' comment regarding tuberculosis, no conclusions can be reached from the one single case included in this report. However, the literature reveals that, although controversy still exists regarding this matter, most authors do not consider incipient, or even active, tuberculosis as a contraindication. Pacella cited 4 cases of latent and active tuberculosis treated with electric shock in which there were no complications and no reactivation of the pulmonary process. Smith reported the case of a middle-aged woman who had active bilateral pulmonary tuberculosis for several years. Fluid in the pleural sac and myocardial disease were present. She received a series of electric shock treatments, not only did she recover from her mental illness, but the pulmonary tuberculosis was said also to have improved.

Patients with disturbances of bony structures and joints can now escape without fractures or dislocations or may have them minimized, with the present method of proper splinting of the torso, limbs and head by means of four or five attendants.

A delicate point arises as to what constitutes advanced age. We treat all patients irrespective of age, treatment being determined by the person's physical

condition. We do not employ curare. It may interest those who are still using this drug that in a review of 11,000 cases in which electric shock was employed, Impastato and Almansí found 8 deaths, 4, or 50 per cent, of which occurred in patients who had received curare prior to treatment. It has been our feeling that this drug adds insult to injury by superimposing respiratory paralysis on the respiratory embarrassment incident to the shock treatment itself.

### Histopathologic Study of an Early Case of Schizophrenia in Which Electric Shock Therapy Had Previously Been Employed DR N W WINKELMAN

A young married woman of 22 was admitted to the Philadelphia Psychiatric Hospital on Jan 16, 1945, was given the usual course of electroconvulsive therapy and was discharged as slightly improved on March 1, 1945. From her history it was learned that she had been born at full term and had weighed 3¾ pounds (1,700 Gm) at birth. She did not walk until the age of 17 months and began to talk much later. As a child she was meticulous and liked to have her own way. She changed schools three or four times because of feelings of inferiority. She married at 19 and gave birth to her only child at the age of 22. After delivery her family and friends noted a complete change in her. She became apathetic and uninterested in her friends and careless in her personal hygiene. She gradually retreated from reality. The diagnosis was schizophrenia.

After her discharge from the hospital the patient seemed to adjust at home, but she worried about her husband, who was in the South Pacific. She committed suicide with gas on April 25, 1945.

Gross examination of the brain showed intense congestion.

Microscopic examination revealed the presence of scattered foci of either devastation or complete loss of cells throughout the frontal, temporal and parietal lobes particularly. There was no evidence of damage to the brain as the result of the electroconvulsive therapy. The carbon monoxide had produced no cerebral damage, since death had occurred within thirty minutes.

The question of a histopathologic picture characteristic of schizophrenia was discussed, with careful consideration of the two schools of thought, the one claiming that the changes observed in brains of patients with dementia precox can be duplicated in normal brains and the other believing that while specific changes do not occur with dementia precox there are alterations which are encountered uniformly.

It was concluded (1) that an assured and satisfactory histopathologic picture for dementia precox does not exist and (2) that the most constant change described in the literature, as in the case reported, is the presence of small focal cortical lacunas, from which groups of cells successively disappear.

DR S DEWITT LUDLUM. The schizophrenic person is a biologically poor organism, why should he not show biologic changes? Why did some patients have heart disease so early? They were in poor adaptability biologically. I see no reason that there should be any quarrel as to the functional or organic nature of schizophrenia. The two go together. If a person is not well put together, he falls victim to some disease.

DR HERBERT H. HERSKOVITZ. I second Dr Winkelman's remark that one should never make up one's mind regarding the cause of schizophrenia until the last word is written. In the first sentence of his summary Dr Winkelman indicated that he does not believe that what he has described in his paper is the last word. Eventually the answer will be found. There is a pathology which also cannot be overlooked and must be studied just as intensely and just as thoroughly as Dr Winkelman has studied the cells of his patient's brain. I refer to psychopathology.

DR. MATTHEW T. MOORE. During the early 1930's I was privileged to perform pneumoencephalographic examinations in 152 cases of various psychoses. Of

these, 71 were cases of schizophrenia. The diagnosis was definitely established, each patient having been seen by the staff and examined carefully before the diagnosis was made. The majority of the roentgenograms in the cases of schizophrenia showed a predilective atrophy of the parietal lobe, with a lesser degree of atrophy in the frontal and occipital lobes. This work has been repeated elsewhere, with the same findings. This week I sectioned the brain of the very first patient on whom I performed pneumoencephalographic studies in 1930. The films in her case showed the type of atrophy just mentioned. On gross inspection her brain revealed definite atrophy of the cerebral gyri. Section of the brain showed definite shrinking of the white matter. The controversy as to whether schizophrenia is a functional disorder or has an organic background still rages. It is generally known that until the latter part of the nineteenth century dementia paralytica was considered a functional disorder, and it was not until the treponema was found in the brain substance and the characteristic pathologic picture of dementia paralytica was established that the organic nature of the disease was accepted. Mott, in the early part of the century, showed that many brains of schizophrenic patients had hypoplastic vessels at the base. The work of many investigators, including Dr. Ludlum, indicates the structural and biochemical disturbances which seem to characterize persons with schizophrenia. The fact that no specific change in the cells of the brain can as yet be demonstrated in these cases does not militate against the assumption that some morphologic or biochemical change may exist in the brain substance. In any event, it is essential to have an open mind regarding such problems. Dr. Winkelman's offering this evening is deserving of credit in that it is a probing study and will serve, I am sure, as a steppingstone to a better understanding of this intriguing, and as yet elusive, subject.

MAJOR M. M. KESSLER, M.C., A.U.S. I am emboldened to make a few remarks which are contrary to the theory presented, because it is generally accepted that schizophrenia is a functional nervous disease without a known pathologic basis. Through significant researches the general conclusion has been reached that the brain of a schizophrenic person presents no demonstrable pathologic change, either grossly or microscopically. On the other hand, there are cases of schizophrenia in which the disorder is superimposed on an underlying organic disease. Schizophrenia can occur with mental deficiency. It is then called a psychosis with mental deficiency. One does not conclude from such a combination that any pathologic condition observed in the brain of a mentally deficient person is the cause of schizophrenia.

In the case presented the patient weighed only  $3\frac{3}{4}$  pounds at birth, indicating that there may have been some abnormality in the child from the time of birth. This was confirmed by the report of general retardation in the early developmental years. Other complicating factors disturb the clarity of this case as one demonstrating the pathologic changes of schizophrenia. Not long before the patient's death she received insulin hypoglycemia and electric shock therapy. These are known to cause an encephalopathy. An additional confusing factor is that the patient committed suicide with carbon monoxide. The history is not clear as to how long the patient lived during the exposure to gas. The anoxemia attendant on this means of suicide could easily result in pyknosis of brain cells and attenuation of cell processes. The reduction of brain cells in certain areas of the brain could be part of an old process which has been present since birth. I feel, therefore, that the author's conclusion must be accepted guardedly. It may well be that in this case the schizophrenic psychosis was merely superimposed on an encephalopathy of unknown origin.

MAJOR THEODORE LIDZ, M.C., A.U.S. Major Kessler's discussion has raised a vital point. It affects not only the paper which has just been read but attitudes which have been prominent throughout the evening. It permits, if it does not lead to, the assumption that some organic means of cure must be found. It fosters the concept that unless some physical measure can be adopted the patient is

incurable It is well to remember that patients with neuroses and psychoses similar to those presented here improved and recovered before shock therapy was introduced

To continue to search for questionable changes in the cortex when another, very gross pathologic condition calls to any careful listener seems to me to lead in the wrong direction Listening day after day to the histories of schizophrenic patients, as one does at the Army psychiatric centers, reveals striking abnormalities of family setting and social development of the individual that are real, factual and concrete, even though they exist only in historical perspective One does not have to peer through a microscope at a brain which may have been damaged by several other traumas to find a pathologic process in schizophrenic patients

It may also be revealing to come to a military hospital where soldiers arrive with records of typical schizophrenic reactions and recover promptly, or to see, as I have had the good fortune to do, patients I have sent home from India whom I thought would never recover because of behavioral patterns that seemed rigidly fixed in negativistic or paranoid constellations, appear totally changed and apparently well after several months in the United States

At the Army general hospital where we are stationed my colleagues and I have month after month seen approximately 70 per cent of the psychotic patients, including those with schizophrenia, return home after several months of hospital care without shock treatment I assure you that we have not been able to offer them elaborate treatment, much as we should like to, because of the pressure of work They receive good care, an active program that keeps them well occupied, but primarily consideration and respect If the change from the jungle to the United States, from despair and frustration to consideration and social existence, can produce a change so profound within a few months, one gets a different impression of schizophrenic reactions and of what may be making these patients ill

DR N W WINKELMAN I am in thorough accord with Dr Ludlum about the poor structural makeup of the schizophrenic patient I believe that schizophrenic persons are born, not made The patient I reported weighed  $3\frac{1}{4}$  pounds at birth Her whole life showed inadequacy, not mental deficiency She got along in school with her studies, but not with her companions After the stress and strain of childbirth, she "broke" and a true schizophrenia developed She committed suicide with gas One can disregard the histopathologic changes due to the carbon monoxide because she died within thirty minutes Death in cases of this sort is a "blood death," due to deprivation of oxygen, it is not a "brain death" Had this patient lived on for twenty-four to forty-eight hours, we should then have had recognizable cerebral damage which would obscure and confuse the changes which we believe may result from the schizophrenic process itself

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## NEW YORK NEUROLOGICAL SOCIETY AND THE NEW YORK ACADEMY OF MEDICINE, SECTION OF MEDICINE AND SECTION OF NEUROLOGY AND PSYCHIATRY

Franklin M Hanger, M D, *Chairman, Section of Medicine, Presiding*

*Joint Meeting, Nov 20, 1945*

### Intravenous Administration of Histamine in Treatment of Migraine

DR WILLIAM A THOMAS and DR STUYVESANT BUTLER, Chicago (by invitation)

Histamine (decarboxylated histidine), released by allergic reactions, remains only momentarily in the circulation and is taken up by the tissues There is no sensitization to histamine in the anaphylactic sense, as it is nonantigenic, but in persons with lower tolerance to histamine this substance reaches shock organs (skin, bronchial tubes, arterioles and capillaries), causing characteristic responses

Migraine is thought by the authors to be such a reaction and has been treated by long-continued intravenous injections of a solution of histamine in an effort to increase tolerance to the substance

Seventy-five patients with severe, indisputably migraine headaches were given 1 mg of histamine base as 2.75 mg of histamine phosphate in 500 cc of isotonic solution of sodium chloride in the form of an intravenous drip. Results showed increasing tolerance and satisfactory results, with permanent complete relief in 30 patients, temporary complete relief in 11, partial relief in 25 and no relief in 9. The authors suggested even longer-continued (twenty-four hour) injections for patients failing to respond satisfactorily to the shorter, four to eight hour, injections.

This paper was published in full in the March 1946 issue of the *Bulletin of the New York Academy of Medicine*, pages 125 to 136.

#### DISCUSSION

DR STANLEY COBB, Boston (by invitation) It is obvious that men who are able to give complete relief in 40 per cent of cases of migraine headache have made a real advance, and I think the speakers of the evening are to be congratulated on that score alone.

I should like to ask about some particulars. In the first place, I am a little skeptical about the relationship of Menière's disease (in the strict sense of the word) to migraine. I think that there is a relation between migraine and spells of vertigo and dizziness, but not classic Menière's disease. Such a distinction is perhaps academic.

Then I should like to ask the authors concerning their statement about the allergic response. They spoke of it as a widely accepted idea that migraine is an allergic response to histamine. I should not say that the idea is widely accepted, and I think from their later words they do not accept it themselves. If migraine is considered, not as an allergic response, but only as a lowered tolerance to histamine, it is easier for me to understand.

The observations on the vessels of the eyeground interested me greatly, for I should think that when they were giving histamine intravenously they would have seen vascular dilatation. In experiments that Dr Wolff and I carried out in 1928 histamine gave a widespread dilatation of all the cerebral vessels. Moreover, I had thought that histamine headaches were caused by a wide dilatation of the cerebral vessels.

I wonder why this remarkable effect is produced by the intravenous administration of histamine and none to speak of by the subcutaneous method. Is there any explanation for that?

DR WILLIAM A THOMAS, Chicago I shall answer Dr Cobb's last question first, that is, the superiority of intravenous injection to the subcutaneous method. I had hoped to make that clear, but I fear I did not. Histamine, regardless of the source of origin, whether injected subcutaneously or intravenously, or produced by some other mechanism, such as heat or cold, remains in the circulation momentarily, no longer. If a constrictor is placed about the upper part of the arm, histamine is formed in the lower part of the arm, and during the time the constrictor is there blood withdrawn from the vein will be shown to contain histamine. If the constrictor is removed, histamine immediately disappears from the circulation. It is taken by the cells so rapidly that there is none circulating. It has been our idea that if one wishes to increase the tolerance of a patient to histamine, rather than give the substance in injections two, three or four times a day, with a brief exposure, necessarily a limited one, because one cannot give doses that will produce shock of any type, one should provide long-continued exposure by giving histamine intravenously for six, ten or twenty-four hours, as fast as the patient can take it. We have found that the patient's tolerance can be raised from taking 3 or 4 drops a minute, and a total of 40 to 50 cc, to 10 drops a minute, and a total of 100 cc, and eventually to the full dose, 1 mg of histamine base.

I hope I have not misstated what we mean by histamine cephalalgia. We believe that headaches which are paroxysmal and unilateral may be a histamine cephalalgia. As I understand it, there is a great deal of discussion as to whether true histamine cephalalgia is due to vasodilatation or to vasoconstriction. We have to deal with many of the manifestations of histamine reactions. The rate at which histamine is given determines entirely what happens. It can be given so slowly that one gets the histamine reaction—the flushing of the face, then of the neck and then of the shoulders—but at the same time there is a vasoconstriction of the lower extremities with a decrease of body temperature as much as 5 degrees (Fahrenheit). The reason I have been so emphatic against the use of histamine as a skin test is the great variability of the reaction. The response to histamine depends entirely on the balance of forces between the vasoconstrictor and the vasodilator mechanism. A reaction before a meal or before ingestion of alcohol will be slight, and that after a meal and after ingestion of alcohol will be great. If two similar doses are injected in the two arms and a blanket is placed over one area, this area will be four or five times as large as the other. An outstanding fact to be considered is that the cutaneous reaction is minimal in brunets, large in blondes and maximal in red-headed persons. Therefore, where the histamine reaction takes place, whether it involves the vessels of the internal carotid artery or not, depends on the rate at which the substance is given, and in patients with migraine one cannot give it fast.

We had no intention of relating Meniere's syndrome to migraine, it was only after Rainey (*J A M A* 122:850 [July 24] 1943) had treated Meniere's syndrome unsuccessfully with subcutaneous injection of histamine that he found he had better results with the intravenous method, I simply stated that he confirmed our point that the intravenous method is superior.

As far as the question of allergy is concerned, I was certain we were going to run into some problems. We came here to discuss the intravenous treatment of migraine with histamine, and not these other ramifications. If the thesis is correct, the \$64 question is where the histamine comes from, and I do not know whether it is allergic or not. We have no intention of stating that it is, I meant to say that it is fairly generally believed that such is the case. We do not subscribe to the idea entirely.

DR HAROLD G. WOLFF. I should like to discuss this interesting and important contribution to the management of migraine headache from two points of view: first, that of the mechanisms of the preheadache phenomena and of migraine headache, and, second, that of the management of migraine headache. The preheadache phenomena constitute the part of the migraine attack itself that is non-painful and consists of visual, and sometimes sensory, disturbances. It has been deduced from evidence obtained in patients that cerebral vasoconstriction primarily within the cranial cavity is responsible for such preheadache phenomena. As far as has been observed, there are no painful components during this phase of the attack. The painful phase is associated with vasodilatation and is related to changes in the amplitude of pulsations of cranial arteries, chiefly the branches of the external carotid artery. Whether the headache stems entirely from structures outside or inside the head can be dismissed for the moment. It is important to emphasize the difference between the preheadache and the headache phase of migraine, for there is no experimental evidence that vasoconstriction inside the head gives rise to pain. The headache phase of migraine has to do with vasodilatation.

If ergotamine tartrate is given during the early part of the painful phase of a migraine attack, it constricts the cranial vessels, chiefly the branches of the external carotid artery, and to a less extent the branches of the internal carotid artery, and is thus successful in eliminating the headache. If it is given late, it usually constricts the vessels less rapidly and less completely, and perhaps not enough for therapeutic purposes.

It was postulated that after the sustained arterial dilatation of a local artery of the head, there occurs a transient change in the structure of the arterial wall,

namely, thickening or edema of the muscular and adventitial structures. Sections of blood vessels of patients with intractable migraine headache were removed while the temporal arteries were being tied off for the relief of pain. In these sections there were found some hints of thickening of the walls, but suitable controls were not available. Experiments were then carried out on the arteries of cat ears. These were studied after prolonged vasodilation produced by infusion for two hours of 10 cc of mammalian Ringer's solution containing a vasodilator agent. The dilated arterial walls were compared with the arterial walls of a control ear by means of serial sections. Measurements demonstrated thickening of the arterial walls of the infused ear. Also, the vasoconstrictor agent, ergotamine tartrate, was found to be less prompt and less effective in constricting arteries with such thickened or edematous walls than arteries with normal walls.

Similar changes in arterial walls of patients during long migraine headaches may be the explanation for the rigid, pipelike texture of the arteries, the steady, aching pain, and the tenderness of these structures. Also, these changes may explain the decreased ability of ergotamine tartrate to reduce the intensity of prolonged headache.

There is a second mechanism of pain during the migraine attack which should also be considered, it involves sustained contraction of the muscles of the head and neck. Pain in the head from any cause induces secondary contraction of these muscles, which when maintained becomes in itself a source of pain. Such painful contractions may outlast for some time the primary cause of the contraction, i. e., cranial vasodilation. This affords an explanation of the failure of ergotamine tartrate to produce relatively prompt relief in some patients who have a major muscle component in their headaches.

The chief consideration, however, and the question so far unsatisfactorily answered, is what makes the cranial vessels dilate—is histamine the agent that causes the dilatation that is so painful? What is the evidence for the role of histamine to date? Important pieces of evidence have been presented by von Storch and by the speakers of the evening. They have observed that in some persons with migraine the injection of small amounts of histamine will more readily induce a headache than in the average person not susceptible to migraine. That is interesting but not conclusive, because in some persons with migraine the ingestion of small amounts of alcohol also precipitates headache. One must therefore wait for more conclusive evidence that histamine is the agent causing vasodilation in the painful phase of the migraine attack.

What is the bearing of all this on treatment and the prevention of migraine attacks? Certainly, the evidence as given tonight indicates that the administration of histamine intravenously in precisely the manner described has dramatic effect. But the interpretation of the results of this method of treatment is difficult. It is easy to observe the success or failure of an agent in terminating an individual attack of headache, but in an illness that is so unpredictable in terms of the next attack, and in such a complicated situation as migraine headache assumes in terms of the patient's life, it is not so easy to evaluate what is going to prevent a headache a week or a month hence. It is interesting, however, that any planned regimen reassures the patient and gives him a conviction of being cared for, which is important in the treatment of migraine.

For example, we have a patient, a woman aged 44, with a history of migraine over many years, who was having an incapacitating headache once or twice a week during July and August. She came into the clinic at the end of August and was given lactose pills and nothing else, except for the assurance that she did not have a cerebral tumor or other serious illness. She was told to take her pills three times a day. During September and October she had no headaches for a three week period, and then infrequent, mild headaches of short duration. That is characteristic—a short-lived effect while the patient is in contact with the physician and with the administration of a symbol of therapeutic significance.

The second case is a little more complicated. The patient was a man aged 48 who had one or two headaches a week during 1936, 1937 and 1938. I had three



interviews with him in 1938. It is not important to discuss what was said except that he was reassured as to the nature of his headaches and his emotional attitudes were considered. Thereafter his headaches stopped until the spring of 1939, when he had a few, and again in the spring of 1941 he had a few attacks. I interviewed him once, and his headaches stopped. He had none during the remainder of 1941 and during 1942 and 1943. In the fall of 1944 he got into a frustrating situation of inactivity in his Navy post, which precipitated a great many headaches, almost daily for a while and always the same. Then an able young physician treated him by means of subcutaneous injections of histamine in the manner described by Horton (*J A M A* **116** 377 [Feb 1] 1941), and this therapy was painstakingly carried out. The headaches then stopped completely but returned again after a few days. He was given more treatment and had no headaches until three months later. He was again given a series of subcutaneous injections of histamine, but the headaches continued throughout the first three months of 1945. I saw him again on April 1, and we discussed matters concerning his attitudes, which were of first rate importance to him, and he has had no more headaches to date (a period of six months). If such is the natural history of patients with migraine, it is evident how exceedingly difficult it is to draw any inferences concerning the effect of a specific therapy. This does not sanction a nihilistic point of view but indicates the difficulty in drawing inferences.

Concerning the percentage of successful effects with various therapies, it is interesting that if one picks at random three forms for which statistics have been given the results are not dissimilar. For the treatment of Balyeat who managed his patients with migraine by taking away certain food substances, the results were practically the same as those of the speakers this evening: 30 per cent excellent, 30 per cent good, 20 per cent fair and 20 per cent failures. Pfeiffer, Dreisbach and Roby (*J Lab & Clin Med* **29** 709-714, 1944), who gave a mixture of calcium lactate and potassium chloride to 150 patients over a period of three years, reported results as follows: 24 per cent excellent, 39 per cent good, 27 per cent fair and 10 per cent noneffective. In other words, they achieved over 70 per cent good and excellent results with an entirely different method of management. In my own series there are 58 patients, of whom 28 per cent had no recurrences in a period of several months to five years, 33 per cent had some headaches, but infrequently and of less intensity, 18 per cent had some improvement, but not very satisfactory, and about 20 per cent had no improvement. The management consisted in reviewing the patient's problems, indicating the nature of migraine, pointing out certain dominant drives in the patients and showing the need for changed attitudes. With this type of therapy I got about the same results as those for the two treatments cited and about the same results as did the speakers of the evening. These statistics on the success of other types of therapy do not indicate that histamine is not the specific agent in causing or preventing migraine headaches. By presenting them, I wish to emphasize again that it is exceedingly difficult to draw inferences, and I do not think that the evidence presented tonight has settled the question as to what causes the painful dilatation of the cranial vessels in migraine headache and whether histamine is the specific therapeutic agent.

**DR MILES ATKINSON** I have been particularly interested in the question of Meniere's syndrome, as you probably know, and I have found that a fairly large number of patients with migraine in the early years of life had Meniere's syndrome in their later years. I do not say by any means the major proportion, but a fairly large number. I presented this material in the paper to which Dr Thomas referred (*Diagnosis and Treatment of Meniere's Syndrome, Arch Otolaryng* **37** 40 [Jan] 1943), and it has been my concept that this group of patients possesses a primary vasoconstrictor mechanism, such as Dr Wolff has described and demonstrated, which in the early years produces migraine—the primary vasoconstrictor, or preheadache, phenomena and the secondary vasodilator, or headache, phenomenon. In the same way, in the case of Meniere's syndrome there is a primary vasoconstrictor group. In this vasoconstrictor group of Meniere's syndrome,

which is the major group, the same thing happens. There is a primary vasoconstrictor disturbance in the inner ear which causes vertigo, then, when the vessel relaxes, the patient gets the aftermath of unsteadiness and quite frequently headache, not migraine headache, not the typical unilateral headache, but headache of one sort or another. I have become so convinced of this that I am accustomed to say that a migraine is Meniere's syndrome in the brain and Meniere's syndrome is migraine in the ear. It was this observation which led to my interest in migraine and to my suggestion that it might be a good plan to try and prevent the primary vasoconstrictor mechanism in migraine by producing vasodilatation, and, as I have been accustomed to use nicotinic acid, not as a vitamin but as a vasodilator, I suggested it might be used to prevent attacks—not to cure the attack in being but to prevent its onset. I published a small series of cases (*Ann Int Med* 21 990, 1944), to which Dr Thomas referred, in which it did seem to have some good effect. I also suggested that histamine might do the same thing, for my view of histamine in connection with Meniere's syndrome and migraine is that it acts not in any recondite manner, but probably simply as a vasodilator. I should like to ask Dr Thomas a question which has been on my mind for some time. I have had no great experience in treating migraine—I just pick up the cases as I find them, and I do not see a great many. I have had no personal experience in treating migraine with histamine, but I have had experience in treating patients with Meniere's syndrome myself and in seeing patients who have been treated by others with intravenous injection of histamine. It has been my experience that it is again the vasoconstrictor group in which one gets a good initial result in relief of Meniere's syndrome, which, as I say, is in my view migraine in the ear, that they will get relief of symptoms for a varying period after the first course of treatment, and that sometimes when they get a relapse a second course will help them, but often a second course will not help them. They get no effect from it at all. I can think of several cases in which no improvement has occurred with a second course of intravenous injections of histamine, and I have found it seems to make the headaches more resistant to the action of nicotinic acid. I should like to ask Dr Thomas whether he has had a similar experience in treatment of migraine.

DR WILLIAM A THOMAS, Chicago. I do not believe that we differ from Dr Wolff in any significant way. It has been my purpose to make myself familiar with his work. I agree with his concept that anxiety and rage, that is, emotional disturbances, are frequently causes of attacks of migraine, and I am sure that all have had about the same results in treating migraine. Twenty years ago, with Dr Joseph Miller, we started treating a series of patients with very severe migraine, we gave them each morning a small wineglassful of grape juice on which we dropped 30 drops of castor oil and followed that with calcium lactate during the day. A large number of these patients had dramatic relief. Dr Wolff has indicated this in his report on Dreisbach's patients, with use of calcium lactate. The difference of opinion exists, of course, very largely in whether the vasoconstriction and the vasodilatation follow one another and whether they are caused by the same mechanism. We are inclined to agree with Dr Wolff that branches of the external carotid artery and the extracranial nerves are chiefly concerned in headache and that those vessels are in a state of vasodilatation when the headache appears. Another point in confirmation is that when one is able to test for histamine in the blood, regardless of the avenue of its entrance, histamine has disappeared by the time the headache begins.

There are two other points which might be brought out in relation to Dr Wolff's discussion. One is that in working with Drs Ivy and Grace Roth, of the Mayo Clinic, it was discovered that histamine has a tremendous capacity for lowering the threshold of pain. Ivy has a pain machine and has found that most patients who receive histamine suffer a great deal more from the headache than does a person with a similar headache not caused by histamine.

I cannot answer Dr Atkinson's question. We have had patients, just as he reports, who have had some primary relief from intravenous injection of histamine,

as he has in cases of Meniere's syndrome and then had no relief from subsequent treatments, and we do not know the mechanism. I should like to ask whether Dr Atkinson knows why the primary vasoconstriction he visualizes causes the pain, or is the total mechanism, with the primary vasoconstriction and the secondary vasodilatation, responsible?

To come back to Dr Wolff's question about histamine. We do not know that is the only cause. We do know these attacks are brought on by emotional and vasomotor instability, as well as by thermal reactions. One of the best explanations I know was suggested when Dr Butler and I first gave this paper in Chicago. It was widely discussed—the type of migraine, the attacks and the frequency—and one person asked, "Can you tell me why there are so many migraine attacks on Sunday, when the patient should not be subject to strain, when it is not a matter of dissipation the night before?" and we were able to answer, "Because so many hot baths are taken on Saturday night!"

DR STUYVESANT BUTLER, Chicago. I have a few words to say regarding these comments.

We have given histamine, Dr Wolff, to a number of so-called normal persons in an attempt to determine whether there is a difference in the secretion of hydrochloric acid in the stomach of ulcer-bearing patients and normal persons and to find whether there is a similar reaction to that found with caffeine. We have given histamine very rapidly to these subjects, much more rapidly than we can give it to patients with migraine. We have obtained no headaches whatever, in spite of the fact that they have had the other signs—the severe flushing of the face, for example—and sometimes have had urticaria, even when they had no history of it. It may be that there is something about these patients that makes them have migraine, whereby they specifically get this dilatation of the branches of the external carotid artery, while the normal, nonmigrainous, person does not.

I am much interested in Dr Wolff's reports of the psychotherapy of these patients. We have seen a number (I personally have seen 5) who have at some time attempted suicide because of the severity of the attack and have seen 3 narcotic addicts who had had every possible type of therapy for their headaches before (and I do not believe that they took to narcotics unless the headaches were very severe), and I do not believe that psychotherapy could have helped them. In our series, the cases of greatest severity were the ones in which the greatest percentage of relief was obtained.

In regard to Dr Atkinson's comments, we have been wondering whether the fact that one of the products of the metabolism of nicotinic acid is histamine may have something to do with the results that he has described, in other words, a continuous giving off to the body of histamine taken in the form of nicotinic acid.

DR HAROLD G. WOLFF. It seems to me that this important work ought to be put into shape so it will be available to every one immediately. It is basic. Would it be possible for the investigators to give an equivalent amount of salt or dextrose to alternative patients with headaches of the same nature, magnitude and severity, under the same set of conditions in their laboratory, as when histamine is administered? I think if the results obtained in the 75 patients treated with histamine could be balanced with results obtained from such controls that it would give much more evidence as to the specific action of histamine.

## Book Reviews

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**Les gliomes infiltrés du tronc cérébral** By Georges Guillain, Ivan Bertrand and Jean Gruner Price, 450 francs Pp 286, with 119 illustrations Paris Masson & Cie, 1945

If evidence is necessary of the outstanding achievements of the French scientists, it is furnished by the magnificent book of Guillain, Bertrand and Gruner, written in the spirit of their masters Charcot and Marie, whom all neurologists may proudly call their masters. A surprising fact is the presentation of this first French postwar book in the usual, fine manner of the Masson publishers.

The book discusses those not infrequently encountered infiltrating gliomas of the brain stem (5 per cent of a series of 250 tumors of the brain) which frequently occur in childhood and present diagnostically misleading signs. Headache, though present, does not indicate that the intracranial pressure is increased with these growths. Papillostasis is absent in 60 per cent of cases. These tumors are accompanied with fever, suggesting the diagnosis of encephalitis or of acute multiple sclerosis, and the signs (hemiplegia or paraplegia associated with cerebellar signs) are not contradictory to such a diagnosis, particularly since sensory disturbances are rare and nystagmus, dizziness and speech disturbances are frequent. There is a remarkable abnormal position of the head. Of the cranial nerves, the anterior group (third, fourth and fifth) are rarely affected, the posterior group (sixth to twelfth) are frequently involved. The course is acute in many cases (two to four months or more) but rarely longer than two years. This fact, together with the fever and the absence of a greatly increased intracranial pressure, accounts for the diagnostic difficulties.

Excellent pathologic descriptions accompany the clinical part of the text, and 119 pictures illustrate the manifold kinds of tumors encountered in the 12 cases of the authors. There may be an isomorphous, nondestructive or eccentric gliomatosis, or the tumor may be rather circumscribed. These gliomas consist principally of unipolar spongioblasts of a pseudoneuronophagic, infiltrative type, most prominent subpially and perivascularly. However, all types of gliomas are represented. Some appear as nodules, indicating a polycentric growth. Surprising in cases of these tumors is the relative intactness of the gray matter, contrasting with the demyelination in the infiltrated areas. The relative intactness of the axons explains the lack of secondary degeneration.

Some predisposing factor, some *faiblesse* of the glia, may aid in the development of the tumor. Of great interest is the discussion on the relation of these infiltrating tumors to some encephalitides, particularly the blastomatous form of Schilder's disease, and to the gliomas in Recklinghausen's disease, to which they have many similarities.

The only therapeutic measure recommended is palliative trepanation, which apparently prolongs the life of the patient.

To their own 12 cases the authors added 80 cases from the literature, citing them in a way that greatly increases the value of the work. It is noteworthy that in the bibliography prior to 1920 one finds two American scientists only (Weisenburg and Spiller), whereas in the bibliography of the past twenty-five years more than forty American names appear, evidence of the great interest in this field of neurology in the United States.

In this book, the authors have attempted to employ a new approach to the complicated problem of the tumors of the glioma group which may help solve some questions of interest to the neurologist.

**Manual of Diagnosis and Management of Peripheral Nerve Injuries** By Lieutenant Colonel Robert A. Groff, M C, A U S, and Lieutenant Sara Jane Houtz (P T) A U S, with introduction by I S Ravdin, M D. Price, \$6. Pp vii+188, with 111 figures. Philadelphia: J B Lippincott Co, 1945.

The high rate of peripheral nerve injury in the second world war presented both a challenge and an opportunity to clinical medicine and medical research, in a field which has been relatively inactive since the first world war. Accordingly, several new books on peripheral nerve injuries have appeared within a short time of each other.

The manual under review was designed by its authors "to provide the physician and physical therapist with a concise text containing the essential facts for the understanding, identification and management of injuries to the peripheral nerves." They may be said to have fulfilled this task well if it is borne in mind that the book is designed for "those individuals with little or no previous experience who have had the problems of nerve injuries forced upon them." To the specialist in physiology, neurology or neurosurgery and to advanced students in these subjects the manual is less valuable, except for its emphasis in the first part on the physiologic basis of nerve reactions under normal and pathologic conditions.

In its nine chapters, which total less than sixty pages, part I, on nerve injuries, discusses readably and swiftly the general principles of the anatomy, physiology and neurology of nerve lesions. It contains brief sections on the reaction of injured nerves, phenomena of recovery and regeneration, operative treatment and post-operative care, including the treatment of causalgias. Some unbalance is introduced through the relatively long sixth chapter, which deals with neurosurgical treatment. Since in peacetime it would hardly be desirable for any but neurosurgeons to carry out the operations discussed therein, much of the chapter, dealing, as it does, briefly with preparation of the patient, anesthesia, position, surgical preparation and instruments and, in about 8 pages, with the technic of exposure and repair, appears to the reviewer to be disproportionate. The authors devote a relatively large space (nearly two and one-half pages and a figure) to a modification of the Tarlov plasma glue technic, which has been used successfully by the senior author, but no mention is made of tantalum sutures or cuff.

The first part is illustrated with twelve drawings. The value of the principal feature which figure 1 illustrates, the composition of a spinal nerve, becomes greatly minimized because an added attempt was made to show the spinal cord in relation to a vertebra. This figure contains errors both in the drawing and in the legend.

Part II of the manual is devoted to the details of clinical examination of peripheral nerve injuries. It is introduced by a short chapter on muscle isolation and the principles and general rules of muscle testing. It contains a brief discussion of functional substitution. The remainder of part II is essentially an atlas, with a minimum of text, dealing with functional examination of regions innervated by the cervical plexus, the brachial plexus, the thoracic nerves, the lumbar and sacral plexuses and the cranial nerves. A highly schematic diagram is included with each section to show the distribution of the nerve groups. Offsetting the defect of such schematic diagrams are seven good, large scale anatomic drawings, showing dissections of the major nerves, muscles and vessels of the face, arm and leg. The detail illustrations, of which there are nearly one hundred, are line drawings and action diagrams, which should, as the authors intend, furnish a guide to the physical therapist for the administration of specific muscle exercises. To the reviewer they are not as satisfying as photographs of illustrative cases.

A brief bibliography and a good index conclude the manual, which should prove valuable to the physical therapist and as an introductory book for clinical practice.

## ELECTRICAL SKIN RESISTANCE TEST IN EVALUATION OF PERIPHERAL NERVE INJURIES

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THE MEASUREMENT of electrical skin resistance has been recommended by Richter and Katz<sup>1</sup> and Jasper and Robb<sup>2</sup> as a practical test in the evaluation of injuries of peripheral nerves. This method, in contrast to the sensory examination, does not depend on the cooperation of the patient. It can therefore be used with uncooperative, or even unconscious, patients and may give objective results in cases of hysteria or suspected malingering. Richter and Katz examined 10 patients with injury of the ulnar nerve and found a correlation of skin resistance with sensory changes in most of them. Of the 27 patients with various peripheral nerve lesions studied by Jasper and Robb, all but 2 showed a correlation of the areas of increased skin resistance with the areas of sensory loss. This method is now being used on a large scale in the evaluation of nerve injuries and in the study of recovery.

\* Aided by a grant from the National Foundation for Infantile Paralysis.

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This paper is a partial report of work done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Columbia University.

This article has been released for publication by the Division of Publications of the Bureau of Medicine and Surgery of the United States Navy. The opinions and views set forth in this article are those of the writers and are not to be construed as reflecting the policies of the Navy Department.

1 Richter, C P, and Katz, D T. Peripheral Nerve Injuries Determined by the Electrical Skin Resistance Method, *J A M A* **122** 648 (July 3) 1943.

2 Jasper, H, and Robb, P. Studies of Electrical Skin Resistance in Peripheral Nerve Lesions, *J Neurosurg* **2** 261 (July) 1945.

after various methods of suture (White and Hamlin<sup>3</sup>, United States War Department<sup>4</sup>) It is felt that the return of an increased skin resistance to normality is an indication of recovery of autonomic function, primarily that of innervation of the sweat glands (Richter, Jasper and Robb)

During the past two years, a large series of peripheral nerve injuries has been studied at the Neurological Institute of New York by a group of investigators working in collaboration with the United States Naval Hospital, St Albans, N Y The extent of the injury has been determined and the course of recovery, both spontaneous and after nerve suture, has been followed The objective was the evaluation of practical methods of studying motor, sensory and autonomic functions In cases of complete and partial denervation and during the course of reinnervation, the extent of reduction of motor function, as defined by a thorough clinical examination, analysis of a moving picture film and chronaxia studies, of sensory function, as defined by clinical examination, and of autonomic function, as defined by electrical skin resistance, has been studied and correlated

This paper presents the results of the investigation of the electrical skin resistance test as a practical means of evaluating dysfunction of peripheral nerves

#### METHODS OF INVESTIGATION

The electrical skin resistance was determined with the improved Dermohmmeter of Jasper<sup>5</sup> The technic used was that described by Richter and his associates<sup>6</sup> and by Jasper<sup>5</sup> and Jasper and Robb<sup>2</sup> Quantitative measurements were not taken regularly, as it proved that the gradient of electrical skin resistance between normal and impaired areas was usually great and the boundaries quite distinct After the area of sensory change was outlined, the electrical skin resistance of the normal areas was determined (basic resistance) The area with a change in resistance was then outlined The instrument has a very wide range of resistance values, and the variable resistor could always be adjusted so as to obtain a large scale deflection of the meter in the normal area In this way significant differences could be seen when they existed Finally, comparison was made always with corresponding areas of the other side The normal pattern of variation in low and high electrical skin resistance of the hands and feet, as mapped out by Richter, Woodruff and Eaton,<sup>7</sup> was also considered carefully

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3 White, J C, and Hamlin, H New Uses of Tantalum in Nerve Suture, Control of Neuroma Formation, and Prevention of Regeneration After Thoracic Sympathectomy, *J Neurosurg* **2** 402 (Sept) 1945

4 Neurological Diagnostic Techniques, United States War Department, Technical Bulletin (TB Med 76), Washington, D C, Government Printing Office, 1944

5 Jasper, H An Improved Clinical Dermohmmeter, *J Neurosurg* **2** 257 (July) 1945

6 Richter, C P, and Woodruff, B G Changes Produced by Sympathectomy in the Electrical Resistance of the Skin, *Surgery* **10** 957 (Dec) 1941 Whelan,

We found that the normal sweating of the subject was usually quite adequate to make possible differentiation between normal and denervated areas when the patient was examined in a fairly warm room. On rare occasions only Furmethide (furfuryl trimethyl ammonium iodide), 2.5 to 5 mg, given subcutaneously, was used to induce sweating and thus to lower a high basic resistance that made comparisons difficult and faulty. It is felt that this drug stimulates sweat glands with intact nerve supply, but not denervated glands (Guttman<sup>8</sup>).

Sensory examination consisted in the testing of tactile sensibility and pain sensations due to pinprick, with the occasional addition of two point discrimination, localization of pain and touch sense and deep pain sensation.

Examination of the motor function in this particular correlative study consisted in the usual clinical observation, supplemented with determinations of chronaxia.

Our material consisted primarily of 87 cases of injuries of the following peripheral nerves: ulnar, median, radial, sciatic, peroneal and tibial. Fifteen cases of injury of the brachial plexus were also studied. In all cases the lesion was distal to the point of junction of the sympathetic fibers with the nerve.

The interval between injury and examination varied, since most patients were brought from overseas. However, many cases of complete nerve section could be studied directly after operative procedures, especially that of "plasma glue suture" (Tarlov<sup>9</sup>).

Although many patients were examined several times in order to follow the course of improvement and the rate of regeneration, the time element involved in this slow process does not permit us to outline the results of testing during the whole course, from injury to complete recovery. However, the results in cases of complete lesions of nerves and in cases of lesions of varying incompleteness can demonstrate the practical value of any test in following a course of regeneration.

In the material to follow, the results of the investigation of motor function, the sensory examination and the skin resistance test are correlated.

Motor function is classified as follows: (1) complete paralysis and complete neuromuscular degeneration, (2) definite drop in chronaxia as compared with the values obtained in a former examination, but no response of muscles to stimulation of the nerve, (3) partial neuromuscular degeneration, with some muscles responding to stimulation through the nerve.

The results of the sensory examination are simplified and classified as anesthesia, hypesthesia and hyperesthesia. Emphasis is placed on the correlation between the electrical skin resistance and the sensory function. Varying degrees of sensory loss in the total sensory area of the nerve are also considered in this correlation.

#### MATERIAL

*Injury to the Ulnar Nerve*—In 10 of the 20 cases of injury to the ulnar nerve the total area supplied by this nerve was anesthetic. In

F. G., and Richter, C. P. Electrical Skin Resistance Technic Used to Map Areas of Skin Affected by Sympathectomy and by Other Surgical or Functional Factors, *Arch Neurol & Psychiat* **49** 454 (March) 1943. Richter and Katz<sup>1</sup>

7 Richter, C. P., Woodruff, B. G., and Eaton, B. C. Hand and Foot Patterns of Low Electrical Skin Resistance. Their Anatomical and Neurological Significance, *J Neurophysiol* **6** 417 (Sept.-Nov.) 1943.

8 Guttman, S. A. Use of Furmethide in Testing Sweat Secretion in Man, *Arch Neurol & Psychiat* **51** 568 (June) 1944.

9 Tarlov, I. M. Autologous Plasma Clot Suture of Nerves. Its Use in Clinical Surgery, *J A M A* **126** 741 (Nov 18) 1944.



7 of these cases there was complete neuromuscular degeneration, recovery being in the beginning phase in the remaining 3 cases. In all but 1 of these cases with complete paralysis and sensory loss there was a definite increase of electrical skin resistance in an area which corresponded fairly well to the area of sensory loss. In the 1 case no change in electrical skin resistance was found.

In 5 cases hypesthesia of the total ulnar area was present. In all these cases signs of motor recovery were apparent. In 3 cases there was a correlating area of increased electrical skin resistance. In 2 cases no change of electrical skin resistance in the ulnar area as compared with surrounding areas could be found, but in 1 case the resistance of the whole affected hand (ulnar, median and radial areas) was decreased as compared with that on the other side.

In 1 case with slight motor recovery part of the ulnar area was anesthetic and another part hypesthetic. The two sections showed equal increases in electrical skin resistance (fig 1A). In another case the ulnar area consisted of a zone of anesthesia and one of hyperesthesia. An increase in electrical skin resistance was present only in the anesthetic area. There were signs of very slight motor recovery (fig 1B). In a case with definite indications of motor regeneration part of the ulnar area was hypesthetic and another part hyperesthetic. Only the hypesthetic area showed increased electrical skin resistance. One area each of anesthesia, hypesthesia and hyperesthesia was found in a case with definite regeneration. The total anesthetic area and parts of the hypesthetic and hyperesthetic areas showed increased skin resistance (fig 1C). In a case with advanced motor recovery the total ulnar area was hyperesthetic. Part of this area showed an increase and the remaining part a decrease in skin resistance (fig 1D).

Thus, anesthetic areas were found in 13 cases. In 7 of these cases there was complete motor paralysis, in 5, beginning motor recovery, and in 1, definite motor regeneration. In 12 cases there was complete correlation of the anesthetic area and the area of increased skin resistance. In 1 case no change in electrical skin resistance was found.

Hypesthetic areas were present in 8 cases. In 4 of these cases slight, and in 4 definite, motor recovery was present. In 5 instances there was a complete correlation of the hypesthetic areas and the area of increased resistance. In 1 case there was a partial correlation, and in 2 no change in the electrical skin resistance of the hypesthetic area was present.

Hyperesthetic areas were found in 4 cases. There were definite motor recovery in 3 cases and slight recovery in 1 case. In 3 cases there was no change in electrical skin resistance in these areas. In 1 case only partial correlation with an area of increased skin resistance was found.

Decrease of electrical skin resistance in the entire affected hand was found in 1 case.

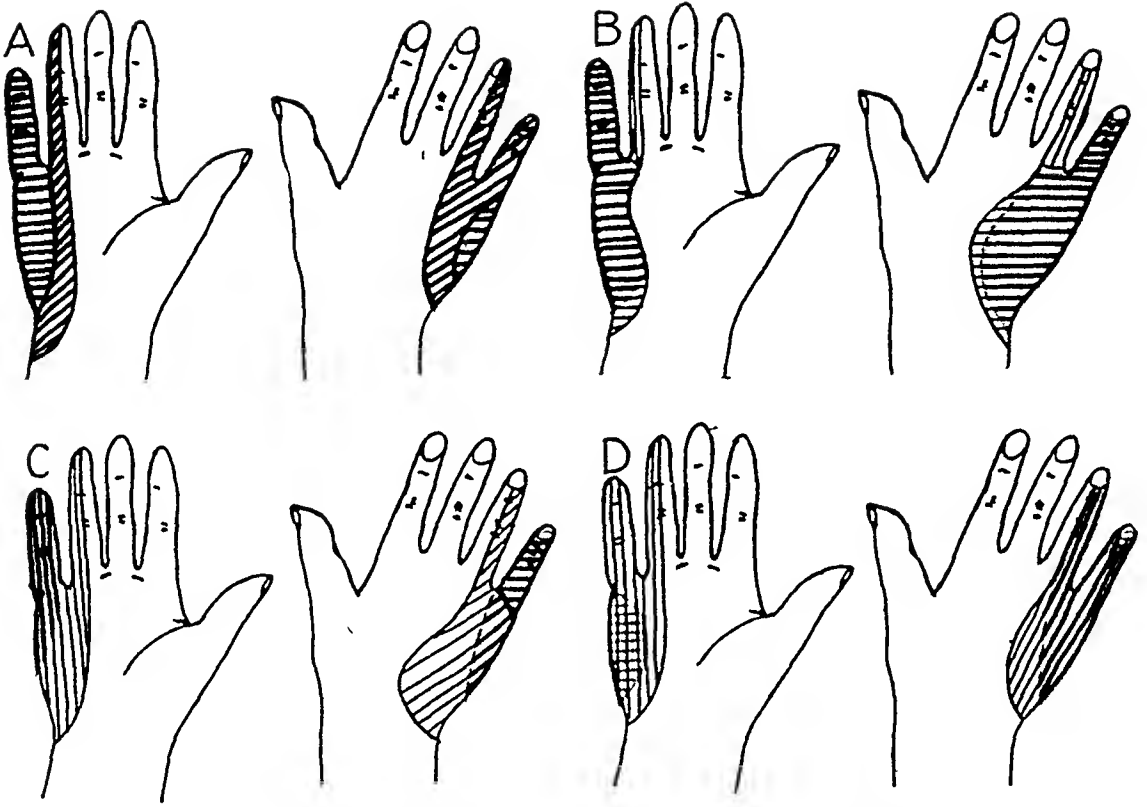


Fig 1—*A*, ulnar nerve injury Part of the ulnar area is anesthetic, another part is hypesthetic. Both zones show increased electrical skin resistance

*B*, ulnar nerve injury, with areas of anesthesia and hyperesthesia The skin resistance is increased only in the anesthetic area

*C*, ulnar nerve injury, with zones of anesthesia hypesthesia and hyperesthesia Increased skin resistance is present in the anesthetic area and in parts of the hypesthetic and hyperesthetic areas

*D*, ulnar nerve injury, with hyperesthesia in the whole distribution of the ulnar nerve Part of this area presents an increase, and another part a decrease of electrical skin resistance

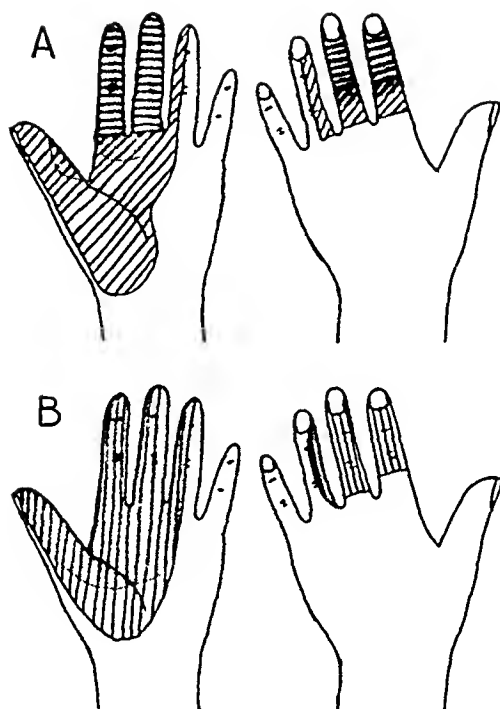


Fig 2—*A*, median nerve injury, with anesthetic and hypesthetic areas In general, the anesthetic area shows increase of electrical skin resistance

*B*, median nerve injury, with hyperesthesia in the total area of the nerve Most of this area shows increase in electrical skin resistance

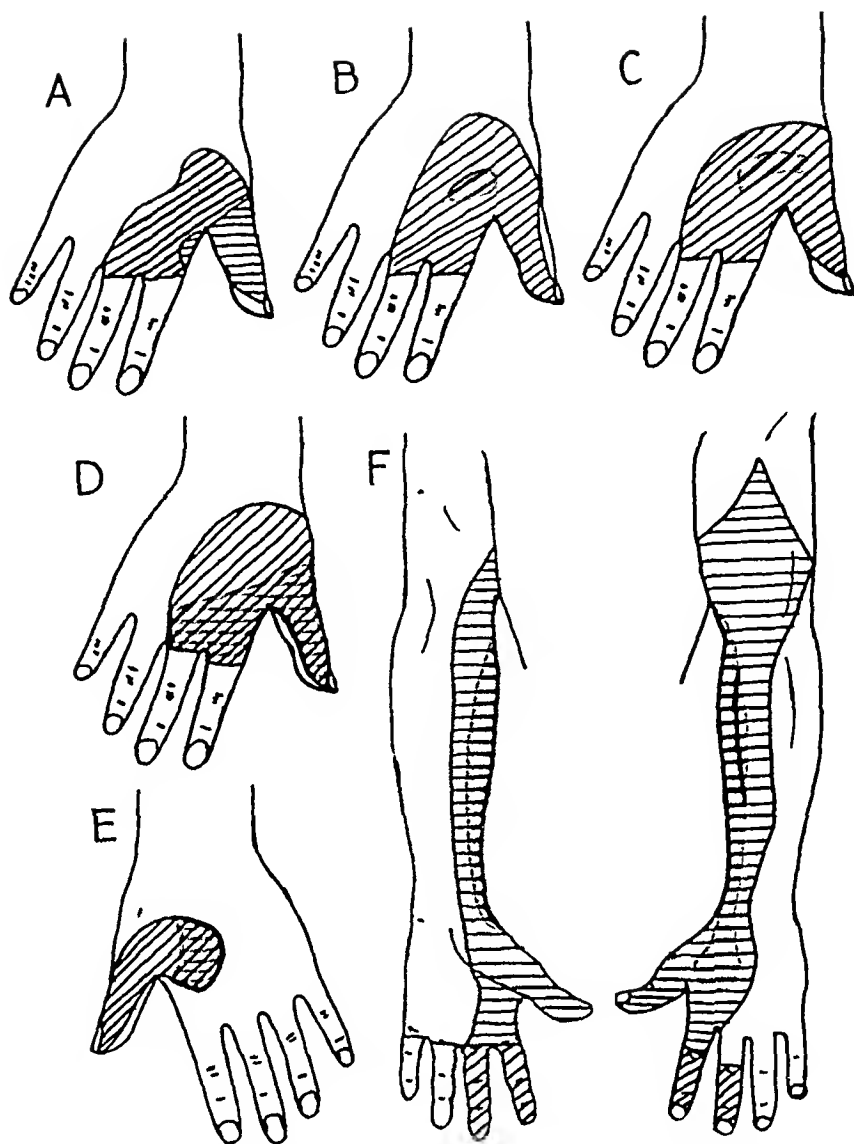


Fig 3—*A*, radial nerve injury, with anesthetic and hypesthetic zones. No change in the skin resistance is present.

*B* and *C*, radial nerve injuries, with hypesthesia and small areas of increased skin resistance.

*D*, radial nerve injury, with hypesthesia and a partial area of increased skin resistance.

*E*, radial nerve injury, with partial area of hypesthesia. Only part of this area shows decrease of skin resistance.

*F*, injury to the brachial plexus with impairment of the median, radial, musculocutaneous and posterior cutaneous nerves.

The area of increased skin resistance in the radial zone is larger than that in cases of pure radial nerve injuries.

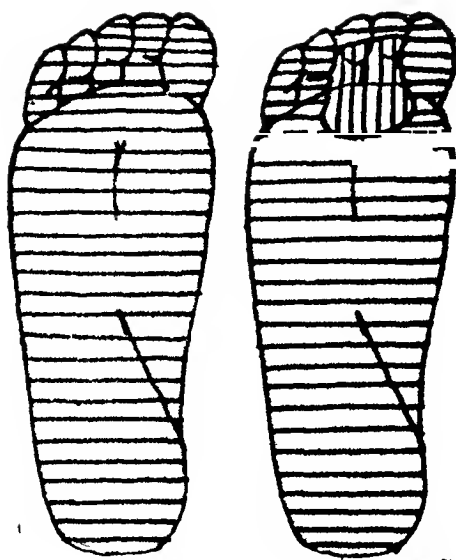


Fig 4—Tibial nerve injury Left, area of anesthesia with correlating increased electrical skin resistance four months after the injury, right, small area of hyperesthesia with normal skin resistance four months after plasma glue suture

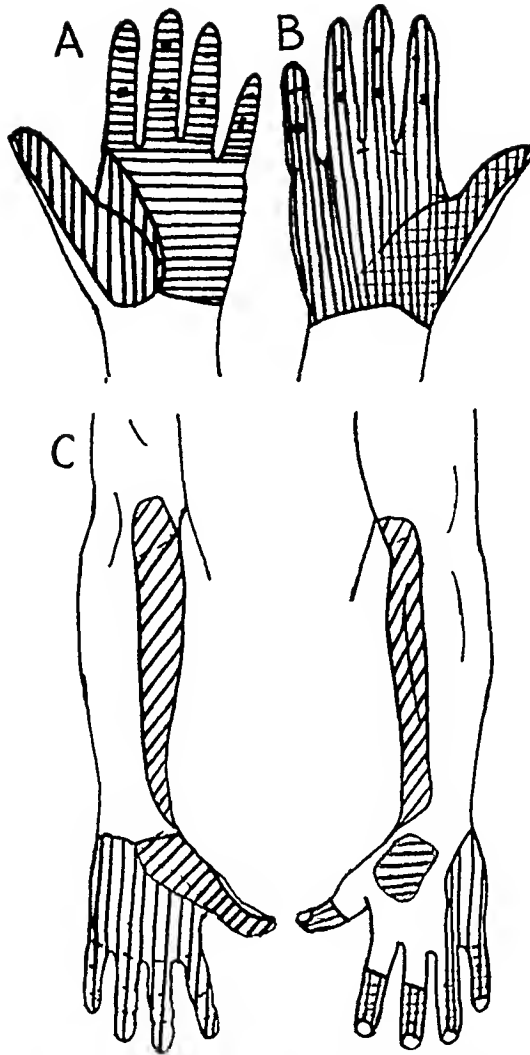


Fig 5—*A*, injury to the brachial plexus, with increased skin resistance in the median and ulnar areas. Part of the median area is hyperesthetic, the remaining part and the ulnar area are anesthetic.

*B*, injury to the brachial plexus with hyperesthesia of the median and ulnar areas. The skin resistance of the ulnar area is increased, the skin resistance of the median area is partly increased, partly decreased and partly normal.

*C*, injury to the brachial plexus with impairment of the musculocutaneous, median, ulnar and radial nerves. The areas of hypesthesia and hyperesthesia do not correspond to the zones of normal, increased and decreased skin resistance.

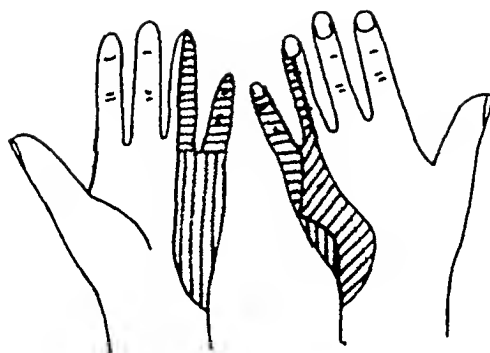


Fig 6—Ulnar nerve injury five months after repair of the nerve Increased skin resistance is present throughout the total ulnar area, with differentiation into anesthetic, hypesthetic and hyperesthetic zones

*Injury to the Median Nerve*—Eighteen cases with injuries of the median nerve were studied. In 6 cases anesthesia of the total area of the nerve was present. In 4 of these cases there was complete motor paralysis with complete neuromuscular degeneration, in 1 case the nerve was in a state of advanced regeneration, and in 1 case no motor impairment was shown. In 5 of these cases there was a complete correlation of the anesthetic area with the area of increased electrical skin resistance. In the case with motor recovery the electrical skin resistance was normal throughout.

In 3 cases areas of both anesthesia and hypesthesia were present in the median zone. In all 3 cases slight or no motor regeneration was shown. All the anesthetic areas showed increased electrical skin resistance. The hypesthetic areas showed increased skin resistance in the whole area in 1 case, there was a partial correlation of the two areas in the second case and no change in skin resistance was found in the third (fig 2A).

In 4 cases the total median area, and in 1 case only part of the median area, was hypesthetic. In all these cases some degree of motor recovery was present. In 3 cases there was a complete correlation of the hypesthetic area with the area of increased electrical skin resistance. In 1 case only part of the area showed increased electrical skin resistance, and in another no change in skin resistance was present.

In 2 cases part of the median area was hypesthetic and another part hyperesthetic. In both cases progressive motor recovery occurred. In 1 case both zones showed increased electrical skin resistance. In the other case the skin resistance of the entire affected hand was decreased as compared with that of the normal side.

In 2 cases in which the total median area was hyperesthetic there was definite motor recovery. In 1 case there was a decreased skin resistance in the entire affected hand. In the other case most of the hyperesthetic area showed an increased resistance (fig 2B).

Thus, anesthetic areas were found in 9 cases. In 6 of these cases there was complete motor paralysis, in 2 cases, slight motor recovery, and in 1 case, no motor changes. In 8 cases there was complete correlation of these areas with areas of increased electrical skin resistance. In only 1 case were there no changes in the resistance.

Hypesthetic areas were present in 10 cases. In only 1 of these cases was there complete paralysis, in 4 cases motor recovery was present. In 5 of these cases there was a complete correlation of the hypesthetic areas with the areas of increased electrical skin resistance. In 2 cases there was only a partial correlation. In 3 cases no change in electrical skin resistance was present.

Areas of hyperesthesia occurred in 4 cases, in all of which definite motor recovery was present. In 1 of these cases there was increased



skin resistance in an area correlating with the hyperesthetic area. In another there was only a partial correlation, and in 2 cases the electrical skin resistance was normal.

Decrease of electrical skin resistance in the whole affected hand was found in 3 cases, in 2 of these the entire median sensory area was hyperesthetic, and in the third it was hypesthetic.

*Injury to the Radial Nerve*—Fifteen cases with injury to the radial nerve were studied.

An area of anesthesia, and this only partial, was found in 1 case. The remaining part of the radial zone was hypesthetic, and the motor function in this case showed remarkable recovery. No change of electrical skin resistance was found in the radial area as compared with that of the surrounding skin, but the resistance was decreased in the whole affected hand as compared with that on the other side (fig 3A).

In 13 cases the total radial area was hypesthetic. In 3 of these cases there was complete paralysis, in 3, only slight motor recovery, and in 7, more advanced motor recovery. In only 5 of these cases could a small area of increased skin resistance be found. This was a small, usually half-moon-shaped area, situated slightly above the triangle between the thumb and the forefinger (fig 3B and C). It was present in 1 case with complete paralysis, in 3 cases with slight motor recovery and 1 case with fairly good motor recovery.

In 7 cases the hypesthetic area did not show any change in electrical skin resistance, and in an additional case a part of the hypesthetic area showed a decrease in skin resistance (fig 3D).

In 1 case only a part of the radial area presented hypesthesia, and part of this area showed a decreased skin resistance (fig 3E).

Hyperesthetic areas were not found in the cases of injuries to the radial nerve.

In 4 cases the whole affected hand presented a decrease of skin resistance as compared with that on the other side.

*Injury to the Sciatic Nerve*—Sixteen cases with injuries to the sciatic nerve were investigated.

In 11 of these cases there was complete motor paralysis, and in 5 motor recovery was in progress. In 12 cases there was complete anesthesia of the total sensory distribution of the nerve. In 4 cases the anesthetic zone was only partial, in 2 of these 4 cases there was hypesthesia in the remaining zone, in 1 case, hyperesthesia, and in 1 case the tibial area was anesthetic and part of the peroneal area was hyperesthetic. In the last case there were complete paralysis of muscles supplied by the tibial nerve and good motor recovery in the distribution of the peroneal nerve.

There was a complete correlation between areas of increased electrical skin resistance and areas of anesthesia in all cases. In only 1 of the cases with partial hypesthesia was the skin resistance increased in this area. In 2 cases with partial hypesthesia, as well as in the 2 cases with hyperesthetic areas, no increase of skin resistance could be found. In 1 case with a hyperesthetic area there was a correlating area of decreased skin resistance.

*Injury to the Peroneal Nerve*—Fourteen cases of injury to the peroneal nerve were investigated.

In 5 of these cases there was complete paralysis, in 2, very slight motor recovery and in 7, advancing motor recovery. In 8 cases the total peroneal area was anesthetic, with complete paralysis in 5 cases and motor recovery in 3 cases. In 7 of these cases there was a complete correlation between the anesthetic areas and the areas of increased skin resistance. In 1 case the area of increased resistance was somewhat smaller than the area of anesthesia.

In 5 cases the whole peroneal area was hypesthetic. In all these cases there was some motor recovery. In 2 cases there was a complete, and in 3 cases only a partial, correlation of the hypesthetic areas and the areas of increased skin resistance. In 1 case with definite motor recovery and a partial area of hypesthesia no change in skin resistance was present. Hyperesthetic areas were not found.

*Injury to the Tibial Nerve*—Four cases of injury to the tibial nerve were studied.

In only 1 was there complete paralysis, motor recovery being present to some degree in the others. In all 4 cases the total sensory area was anesthetic and there was a complete correlation of this area with an area of increased electrical skin resistance.

In no case of peripheral nerve injury in the lower extremity was there decrease of skin resistance in the entire affected extremity as compared with that on the other side.

*Injury to the Brachial Plexus*—Fifteen cases with injuries to the brachial plexus were studied. Various combinations of complete or partial injuries of the several nerves of the upper extremity were found, but the degree of motor, sensory and autonomic function varied to such an extent that a statistical evaluation seemed impossible. However, certain cases of this series have been used when particular questions could be clarified.

#### COMMENT

The practical value of the electrical skin resistance test in the evaluation of peripheral nerve injuries depends on the information it gives in addition to the results of examinations of the motor and sensory status. The present investigation was concerned therefore with the

correlation of impairment of the autonomic nervous system, as found with the electrical skin resistance test, with changes in motor and, particularly, sensory function. It has been assumed, predominantly on the basis of the results of sweating tests, that the sensory and the autonomic fibers have a common course in the mixed peripheral nerve and supply approximately the same area of the skin. The question then arises whether the two tests, sensory examination and electrical skin resistance test, yield similar results under the same conditions, whether one test can be substituted for the other or whether the results of the two tests really supplement each other and the variations between the two warrant a careful evaluation of the situation caused by complete or partial nerve injury. In former investigations the degree of sensory loss was somewhat neglected in the correlation of impaired sensory and autonomic function.

In the present evaluation, 87 cases of injuries of the ulnar, median, radial, sciatic, peroneal and tibial nerves were used. Areas of complete sensory loss were found in 51 cases. In 47 of these cases a correlating area of increased skin resistance was shown. This almost complete correlation confirms the findings of Richter and Katz<sup>1</sup> and Jasper and Robb<sup>2</sup> and demonstrates the value of the electrical skin resistance test in mapping anesthetic areas caused by peripheral nerve injuries.

The evaluation of the results of testing hypesthetic areas is rather complicated. In 40 instances areas of merely partially impaired sensory function were found. In 13 of these cases an area of increased skin resistance coincided with the hypesthetic area. In 11 instances there was only a partial correlation, and in 16 cases no change of skin resistance could be found. This discrepancy between the results of the sensory examination and those of the skin resistance test cannot be neglected. It implies that nerve lesions which are partial, either because the nerve injury was incomplete or because regeneration has taken place, may affect sensory and autonomic functions, respectively, in varying degrees.

The most plausible assumption might be that impairment or recovery of sensory and that of autonomic function have not run parallel. If, for instance, the electrical skin resistance of an area is normal, one might assume that autonomic function has been restored whereas sensory function is still defective. This information would be valuable as an indication of some continuity of the nerve or of some progress in repair. Furthermore, in some cases it was found that the area of increased skin resistance was definitely smaller than the hypesthetic area. Again, it could be stated that partial persistence or restoration of autonomic function existed. These significant conclusions might be justified to some extent when serial tests have been made, but on the occasion of the first examination one should avoid premature conclusions.

Hypesthesia is regarded as evidence of partial impairment of the nerve. But in cases of complete motor paralysis of the radial nerve and known complete section of the nerve, as in cases in which examination was made a short time after plasma glue suture with revision of both nerve ends, only hypesthesia was present in the radial area. The time interval was too short for any sensory regeneration to have taken place, although there may have been "overlap." Of these 8 cases of pure radial nerve injuries a very small area of increased electrical skin resistance was present in only 5. This area might easily have been overlooked (fig 3 *B* and *C*).

Foerster,<sup>10</sup> after studying the great individual variations in the cutaneous area supplied by the radial nerve, concluded that this nerve does not possess a constant autonomous area. The neighboring areas of the ulnar, median and dorsal and lateral antibrachial cutaneous nerves apparently "overlap" the area of the radial nerve to a varying degree. The small half-moon-shaped area of increased resistance which we found coincides with the area of anesthesia which Foerster found in some of his cases. The area of increased resistance in the zone of the radial nerve may become larger when the neighboring nerves are involved. In a case of injury to the brachial plexus (fig 3 *F*) a larger area of increased electrical skin resistance was demonstrated in an extensive area of sensory loss due to involvement of the median, radial, posterior cutaneous and musculocutaneous nerves.

It would seem, therefore, that there is sufficient evidence to indicate not only that the sensory area of the radial nerve is variable and lesions of this nerve cause mainly a hypesthesia, but also that the autonomic fibers are few and lesions of this nerve alone do not produce areas of increased skin resistance in a large proportion of cases. The absence of changes in electrical skin resistance in cases of injuries to the radial nerve is thus of no significance.

In instances of injuries of other nerves hypesthesia may also not be due to partial impairment or to regeneration of the nerve which supplied this area with sensory fibers. The affected nerve may be completely injured but part of the sensory area may be functioning to some extent. Foerster<sup>10</sup> differentiated between the "autonomous areas," exclusively supplied by one nerve, and the "maximal area," which remains when all neighboring nerves to this region are severed. The term "mixed" or "intermediate area" is applied to the zone of multiple sensory innervation. The "subsidiary area" of a nerve is that region of its sensory innervation aside from its autonomous area (i e., the extension into the "mixed area"). The difference between

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<sup>10</sup> Foerster, O, in Lewandowsky, M. Handbuch der Neurologie, Berlin, Julius Springer, 1929, supp, pt 2.

autonomous areas and maximal area, or the average extension of sensory defects, as elaborated from various multiple nerve lesions, is shown in figure 7 (from Foerster<sup>10</sup>) Pollock<sup>11</sup> and Weddell, Guttman and Guttmann<sup>12</sup> pointed out that soon after nerve section the area of sensory loss undergoes progressive shrinkage. This shrinkage was regarded as due to "overlap" and concerns chiefly the fibers for pain sense. This situation was further studied by Guttman and Highet,<sup>13</sup> who found that this "progressive shrinkage of the area of sensory loss by nerve overlap [occurs] at a time when there was no possibility of true recovery by regeneration." It was also noted by Guttman<sup>14</sup>

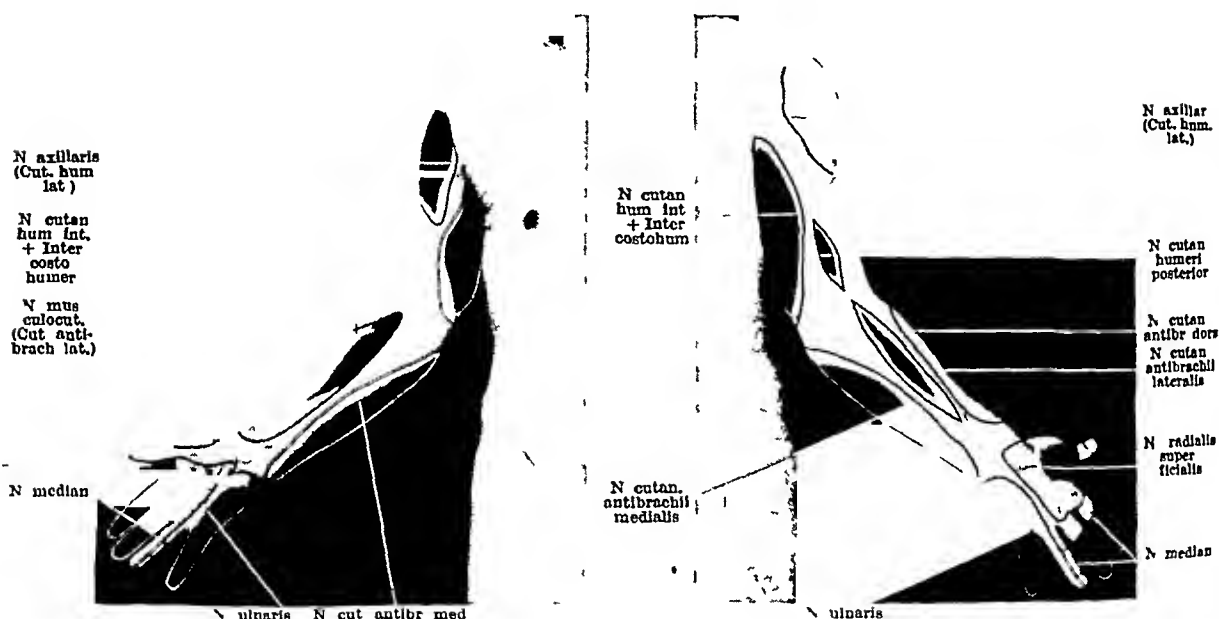


Figure 7

that the overlaps of pain sensation and sweating function are "conspicuous and similar." Guttmann and Guttman<sup>15</sup> finally concluded,

11 Pollock, L. J. Nerve Overlap as Related to the Relatively Early Return of Pain Sense Following Injury to the Peripheral Nerves, *J Comp Neurol* **32** 357 (Dec.) 1920

12 Weddell, G., Guttman, L., and Guttmann, E. The Local Extension of Nerve Fibers into Denervated Areas of Skin, *J Neurol & Psychiat* **4** 206 (July-Oct.) 1941

13 Guttman, L., and Highet, W. B., cited by Highet<sup>16</sup>

14 Guttman, L. Topographic Studies of Disturbances of Sweat Secretion After Complete Lesions of Peripheral Nerves, *J Neurol & Psychiat* **3** 197 (July) 1940

15 Guttmann, E., and Guttman, L. Factors Affecting Recovery of Sensory Function After Nerve Lesions, *J Neurol & Psychiat* **5** 117 (July-Oct.) 1942

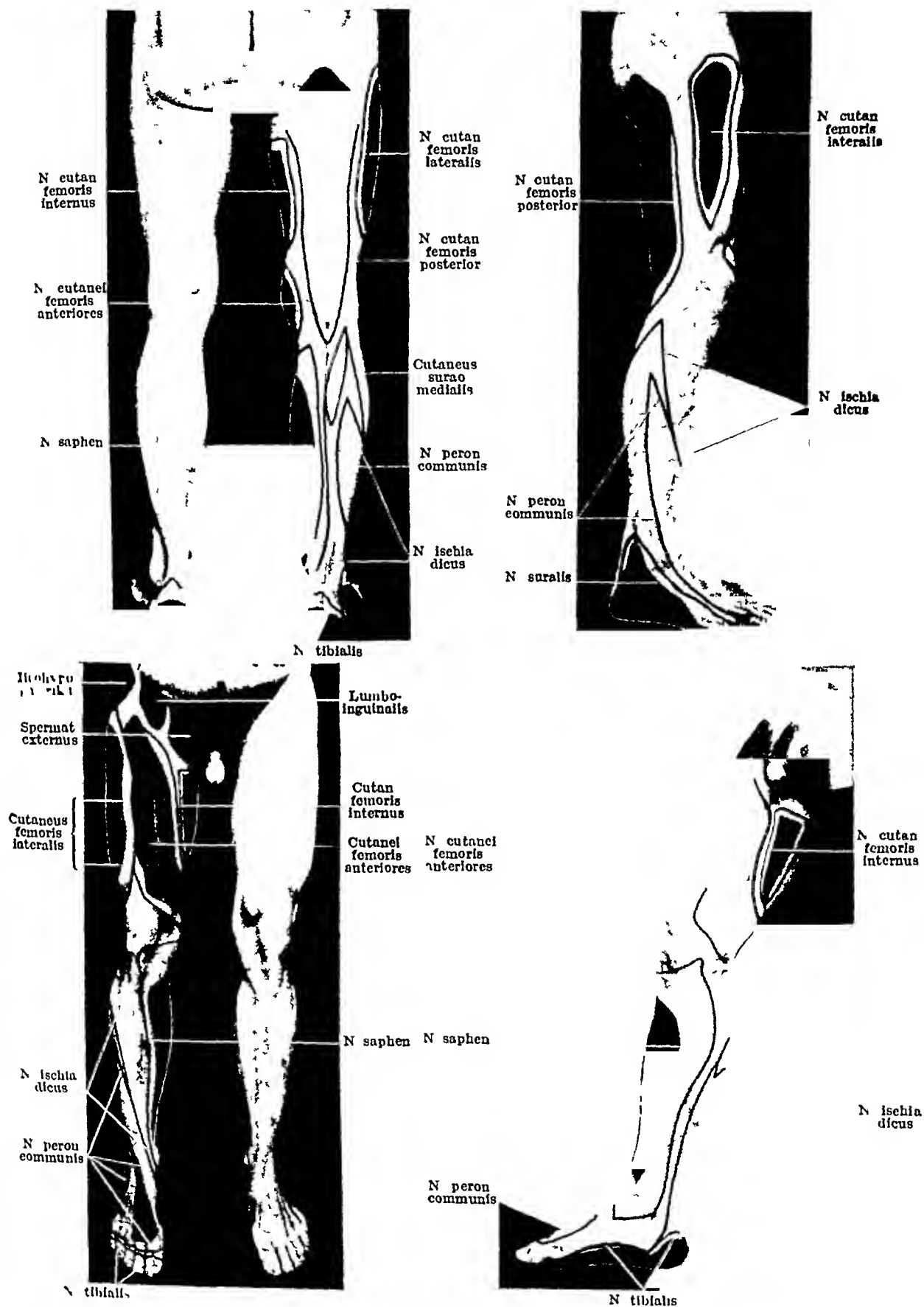


Fig 7—"Autonomous" and "maximal" sensory areas (after Foerster<sup>10</sup>)

by means of animal experiments, that the complex process of recovery of sensation has three components

1 "Recovery" in zones of "overlap," or intermediate zones, by the resumption of "readjustment" of function by fibers of adjacent nerves. The nature of this process is at present obscure and is fully discussed by these authors

2 Anatomic extension of fibers from adjacent nerves into the denervated area, even into the autonomous zone. This extension of neighboring nerve fibers into the area of the interrupted nerve was demonstrated histologically in animal experiments by Wedell, Guttmann and Gutmann<sup>12</sup>

3 Regeneration of the interrupted nerve, or "true" sensory regeneration

Higbet,<sup>16</sup> using a technic of peripheral nerve block with procaine and especially blocking the neighboring nerves of the nerve in question, studied the difference in size of the maximal and autonomous zones and the problems of anomalous sensory loss and "recovery" by means of "overlap"

The aforementioned findings are extremely important in the evaluation of hypesthetic areas and of areas without increase in the electrical skin resistance in the distribution of an injured nerve. Thus, restoration of sensory and autonomic function may be due to subsidiary function (physiologic or anatomic overlap) of neighboring nerves, particularly when it is found in intermediate areas and encroaching only on the autonomous area. Furthermore, it is quite possible that sensory and autonomic functions may be reinnervated in this manner in a variable or nonparallel degree. Consequently, the reappearance of normal electrical skin resistance need not be always or solely due to true regeneration of the autonomic nerve fibers. The case in figure 4 is an example of the possibility of subsidiary autonomic function of the neighboring nerve. The tibial nerve was injured on Feb 23, 1945. Figure 4, left, shows the area of anesthesia and increased electrical skin resistance found on June 15. In July 1945 a plasma glue suture was performed. On Nov 6, 1945 the patient was reexamined, and a small area of hyperesthesia was found on the plantar surfaces of the second and third toes and the interspace between these toes, skin resistance was normal in a correlating area (fig 4, right) which is probably a subsidiary area of the distribution of the deep peroneal nerve. In these instances only investigation of the neighboring nerves with the nerve block technic could clarify the situation and demonstrate the true innervation of the area in question. Furthermore, the extent of

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16 Higbet, W B. Procaine Nerve Block in the Investigation of Peripheral Nerve Injuries, *J Neurol & Psychiat* 5 101 (July-Oct) 1942

the autonomous areas of the autonomic distribution of the peripheral nerves has still to be determined more definitely. Thus, one can conclude that the presence of an area of normal skin resistance in the distribution of an injured nerve is not a definite indication of a partial lesion or a sign of regeneration.

In 10 cases hyperesthetic areas were found. In 5 cases the electrical skin resistance was normal. In 2 cases the hyperesthetic area coincided with the area of increased skin resistance, and in 1 case there was only a partial correlation. In 1 case the hyperesthetic area showed a decrease of skin resistance. In 1 case in which the total ulnar area was hyperesthetic zones of both increased and decreased skin resistance were present in this area. In addition, in 2 of these 10 cases the whole affected hand showed a decreased skin resistance.

In some cases of injury of the brachial plexus with hyperesthetic zones the correlation of the sensory status and the skin resistance was complicated. Three cases will illustrate this problem. In case 1 (fig 5 *A*) the skin resistance was increased in the median and ulnar distribution, but part of the median area was hyperesthetic and the remaining part and the ulnar area were anesthetic. In case 2 (fig 5 *B*) there was hyperesthesia of the median and ulnar areas of the entire palm, the skin resistance of the ulnar area was increased, and that of the median area was partly increased, partly decreased and partly normal. In case 3 (fig 5 *C*), an instance of injury to the brachial plexus with impairment of the musculocutaneous, median, ulnar and radial nerves, the areas of hypesthesia and hyperesthesia did not correspond to the areas of normal, increased and decreased skin resistance.

From our findings it can be concluded that there is no definite relation between changes in electrical skin resistance and areas of hyperesthesia.

A decrease in skin resistance of the affected area as compared with that of the surrounding areas of the same extremity was found in only 4 cases, in all of which definite motor recovery took place. In 2 of these cases the sensory areas were hyperesthetic, and in the other 2, hypesthetic. A decrease in skin resistance of the entire affected hand occurred in 8 cases (4 of radial, 3 of median and 1 of ulnar nerve injury). In all these cases there was evidence of motor and sensory recovery. In 6 instances there was hypesthesia, in 1 case hyperesthesia, and in 1 case both hyperesthetic and hypesthetic areas were present.

Thus, there are two types of circumstances in which decrease in skin resistance occurs, different underlying mechanisms may be responsible. It is quite possible that during the course of regeneration an "irritative" process causes autonomic hyperfunction in the area of distribution of the involved nerve. When the entire hand is involved, a



more complex "reflex" mechanism may play a role (Guttmann<sup>14</sup>), but the nature of such a mechanism is quite uncertain

An attempt was also made to correlate autonomic with motor function. In the series of 87 cases there were 36 with complete neuromuscular degeneration. Of the 47 cases with anesthetic zones and complete correlation with skin resistance, neuromuscular degeneration was complete in only 29, there being signs of motor recovery in the other 18 cases. This indicates that motor recovery, as evaluated by chronaxia, may be an earlier and more sensitive indicator of nerve regeneration. In 51 cases there was evidence of motor recovery and no real correlation with sensory or autonomic function. It should be mentioned that anomalous innervation of muscles by neighboring nerves or supplementary and "trick" movements and local extension of nerve fibers (from neighboring nerves) into denervated muscle (Van Harreveld<sup>17</sup>) must be considered when motor recovery is being evaluated. The nerve block technic of Highet<sup>16</sup> may also be used to solve these problems.

*Course of Regeneration*—The entire course of regeneration, from the time of injury to the complete restoration of function, could not be evaluated in this series, as insufficient time has elapsed. However, the investigation of intermediate stages revealed certain principles which should be valuable in further studies. It is evident that all three functions—motor, sensory and autonomic—should be considered significant, as it has been shown that in many cases there is no correlation in the degree of recovery of these functions. Generally, recovery of motor function seems to be the earliest sign of regeneration, particularly in cases of injury to the nerves of the lower extremity, but also to some extent in cases of high lesions of nerves of the upper extremity in which the distance between the lesion and the muscles to be reinnervated is shorter than that between the lesion and the sensory-autonomic areas. Also, as previously discussed, the restoration of sensory and autonomic function in the area of the distribution of a certain nerve may not necessarily indicate regeneration of sensory and autonomic fibers of the injured nerve.

Increased electrical skin resistance was in all cases an indication of injured nerve function. The lack of increased skin resistance in the distribution of a definitely injured nerve does not necessarily mean the appearance of regeneration, it was noted especially with total injuries of the radial nerve and with partial lesions of other nerves.

In some cases the sensory examination revealed definite signs of recovery, whereas the skin resistance remained as high as before.

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17 Van Harreveld, A. Re-Innervation of Denervated Muscle Fibers by Adjacent Functioning Motor Units, *Am J Physiol* **144** 477 (Sept.) 1945

In a case of complete ulnar nerve injury at the wrist examination, five months after repair, showed that skin resistance was increased to the same degree throughout the entire ulnar area but that there were zones of hypesthesia and hyperesthesia, in addition to a small area of anesthesia (fig 6)

The appearance of a decrease of skin resistance in the area of an injured nerve might be an indication of definite regeneration, but enough data of this type have not yet been collected to warrant definite conclusions. Thus, examination of skin resistance alone does not always give the entire available information concerning the degree of regeneration at a given time. Serial qualitative and, especially, quantitative studies of the degree of increase and diminution of this value during recovery will lend a higher accuracy to the use of the electrical skin resistance test.

Foerster<sup>10</sup> has pointed out that the restitution of sensory function requires a much longer time than motor function. There is nothing known as yet about the regeneration of autonomic fibers except for the work of Neumann, Grundfest, Berry, Rule and Cohn,<sup>18</sup> who showed that after the section and suture of the sciatic nerve of the cat fifteen to thirty weeks elapsed before the first signs of sweat production were observed. The complicated situation with partial nerve injuries and during regeneration indicates that one should not rely too much on the results of the skin resistance test until more is known about the rate and mode of autonomic regeneration.

#### SUMMARY

The electrical skin resistance test was evaluated in 87 cases of injuries of the median, ulnar, radial, sciatic, peroneal and tibial nerves. An additional 15 cases of injuries of the brachial plexus were studied. The results of the skin resistance test were correlated with the degree and area of sensory impairment and the degree of motor dysfunction.

In cases of complete nerve injury the area of increased electrical skin resistance coincided well with the area of sensory loss and the degree of motor paralysis. The skin resistance test is therefore valuable in mapping anesthetic areas.

In cases of partial nerve lesions, due either to incomplete injury or to some degree of recovery, there was no regular correlation of the electrical skin resistance, the hypesthetic or hyperesthetic areas and the motor status. Fundamental physiologic and anatomic mechanisms responsible for this irregularity are discussed.

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<sup>18</sup> Neumann, C, Grundfest, H, Berry, C M, Rule, C, and Cohn, A E. Return of Function of Sweat Glands After Cutting or Crushing Sympathetic Nerves, *Proc Soc Exper Biol & Med* 54:27 (Oct) 1943.

The appearance of decreased electrical skin resistance in the area of distribution of the injured nerve and the whole affected hand is discussed

Certain principles in the evaluation of the course of regeneration with the skin resistance method are considered

The electrical skin resistance test does not give definite information for the diagnosis and evaluation of partial dysfunction of peripheral nerves. In our material examination of motor and sensory functions revealed more practical data. However, the continued study of the electrical skin resistance can certainly advance knowledge of autonomic innervation.

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# PRIMARY BEHAVIOR DISORDERS AND PSYCHOPATHIC PERSONALITY

## I Correlations of the Electroencephalogram with Family History and Antecedent Illness or Injury

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AND

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IN PREVIOUS publications concerning the electroencephalographic evaluation of primary behavior disorders in children<sup>1</sup> and of psychopathic personality in adults,<sup>2</sup> we reported correlations with age, sex, family history and antecedent severe illness or cerebral injury of early childhood, which previously had not been considered of etiologic significance. Statistical analyses revealed that electroencephalographic abnormality was unrelated to age and sex but was related to either a "positive" family history or a personal history of cerebral trauma or severe illness. The inference was that the abnormal electroencephalogram was of either genogenic or histogenic origin and thus represented some aspect of the neural limits of the organism. The original number of patients under study has been increased, thus permitting more complete statistical analyses, from which further implications may be drawn. The present communication has this for its purpose.

Because of the consistency of the findings in the two previous studies and the clinical similarities of the two diagnostic groups, study of the groups singly and in combination would seem warranted. The patients designated as having primary behavior disorders were characterized, in the main, not by a single simple habit or disturbance of conduct but by a multiplicity of these disturbances. Only the patients with the more serious behavioral problems were brought to the hospital, as those with

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1 Gottlieb, J S, Knott, J R, and Ashby, M C. Electroencephalographic Evaluation of Primary Behavior Disorders in Children. Correlations with Age, Sex, Family History and Antecedent Illness or Injury, *Arch Neurol & Psychiat* 53 138-143 (Feb) 1945

2 Knott, J R, and Gottlieb, J S. Electroencephalographic Evaluation of Psychopathic Personality. Correlations with Age, Sex, Family History and Antecedent Illness or Injury, *Arch Neurol & Psychiat* 52 515-519 (Dec) 1944

the less severe disorders had been cared for by various therapeutic agencies. As a result, then, the groups of patients designated as having either primary behavior disorders or psychopathic personality were characterized on the behavioral level by outspoken social maladjustment, which had been either continuous or repeatedly recurrent over a relatively long period. The chief symptoms were one or more of the following: delinquency and law breaking, socially unconventional behavior, emotional instability or other affective liabilities and/or aberrant sexual behavior. There were stereotyped deviations in the moral, social, sexual and/or emotional components of their personalities. The maladjustment in the patients of both groups, furthermore, was not attributable to defects in intelligence, structural diseases of the brain, epilepsy, psychoneuroses or psychoses.

These two diagnostic groups were separated arbitrarily on the basis of age, disturbances in patients of 16 years or above being considered as psychopathic personality and disturbances in patients of 15 years or below as primary behavior disorders. Thus, on a descriptive level, the concept of psychopathic personality became an extension of the concept of primary behavior disorders in children with reference to the age factor—this, irrespective of the recognition that the prognosis for some members of the younger group was better than the prognosis for members of the older group—a difference which may be related to therapeutic intercession nearer the origin of the behavioral difficulty, to the plasticity of the developing personality of a younger person, in contrast to the rigidity of the personality of the older one, and/or to the differences in etiologic composition of the constellations of factors leading to the development of these categories.

The definitions are so broad as to be indicative of a heterogeneous collection of disturbances in behavior and cannot be considered adequate for clinical entities. Both primary behavior disorders and psychopathic personality may be considered categories composed of a number of conditions. The composition of each category in terms of the types of clinical conditions and their relative proportions may, and probably do, vary. By comparative studies, differences may be obtained and evaluated, with the ultimate expectation of better definition, etiologic, as well as descriptive, of better understanding of the composition of the categories, and, possibly, of segregation of clinical entities.

#### METHOD

The present method of study has been described in considerable detail elsewhere<sup>3</sup>. Here it has been applied to 100 patients with primary behavior disorders and 100 patients with psychopathic personality for whom detailed psychiatric, physical, neurologic, laboratory, psychometric and social records had been

3 Gottlieb, Knott and Ashby<sup>1</sup> Knott and Gottlieb<sup>2</sup>

obtained. These patient populations were maintained as homogeneous as possible by the exclusion of all with questionable diagnoses. No patient was included whose symptoms were suspected of being related to epilepsy, psychoneurosis, psychosis or sequelae of a physical illness or injury or whose intelligence quotient was below 80.

Certain data were selected and used as criteria for the designation of the family history as positive. There were four ancestral types which thus could be clearly defined and labeled on the basis of the presence of one of the following conditions: (1) psychosis, (2) maladjusted personality, (3) chronic alcoholism and (4) epilepsy. The use of the term "psychosis" needs no explanation except to say that in many instances the type of such disorder could not adequately be determined through the use of the historical method. The term "maladjusted personality" was applied to those relatives for whom there was evidence of severe social maladjustment (nonpsychotic) and in whom there was apparent difficulty in emotional control. Although the term "psychopathic personality" could not be used, as few of the antecedents had had clinical examinations, the descriptions of their personalities and the histories of their apparent chronic inadequate adaptation to society resembled this diagnostic category. Chronic alcoholism was almost always only one aspect of a severe personality disturbance. In fact, the personalities and the types of adjustment of persons with chronic alcoholism resembled those of the patient designated as "maladjusted personality." Only the chronic addiction to alcohol allowed their designation in a separate category. The term "epilepsy" needs no explanation.

The antecedent illnesses and injuries which were selected were: (1) prematurity, (2) birth injury or questionable birth injury (actually no definite instance was included, the cases placed in this category were all in question, the historical evidence indicating mainly prolonged labor or difficulty in delivery), (3) head injury complicated by unconsciousness, (4) severe illness complicated by delirium, coma or severe stupor (on the basis of the historical material, these illnesses could be divided into very severe and moderately severe, the term "very severe" referring to those illnesses complicated by delirium or coma and meningeal irritation and followed by regression in development and the term "moderately severe" referring to those illnesses complicated by only delirium or coma), (5) convulsions in infancy not considered epileptic in origin, and (6) a period of anoxemia, either at birth or later in life.

Six lead electroencephalograms were obtained with a Grass ink-writing oscillograph in the usual way from virtually all the patients (for the small minority three lead records were made). The records of the patients 15 years of age or under were classified according to the method described in a previous publication.<sup>1</sup> Essentially, the records were classified as normal or other than normal, depending on their similarity to age frequency limits of neurologically screened normal children, as determined by Lindsley<sup>4</sup> and Gibbs and Gibbs.<sup>5</sup> If the frequencies were within these defined limits, the record was considered as normal. If in addition there were some nondominant too slow or too fast frequencies, the record was considered as questionably normal. (Such records were not included in the final statistical treatment of these data because of their uncertain allocation.) If the

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4 Lindsley, D. B. A Longitudinal Study of the Occipital Alpha Rhythm in Normal Children. Frequency and Amplitude Standards, *J. Genet. Psychol.* **55**: 197-213 (Sept.) 1939.

5 Gibbs, F. A., and Gibbs, E. L. *An Atlas of Electroencephalography*, Cambridge, Mass., Lew A. Cummings Co., 1941.

dominant frequencies were above or below the age norm recurrently, continuously or paroxysmally, the record was classified as abnormal. The records of the patients 16 years of age or over were classified according to the frequency scale of Gibbs, Gibbs and Lennox.<sup>6</sup> A 97 per cent agreement was obtained by one of us (J R K) with the ratings of Dr F A Gibbs on the rereading of records which he loaned to us.

All records were obtained from the patients in the waking state, with closed eyes but without hyperventilation.

DATA

The electroencephalograms for both the 100 patients with primary behavior disorders and the 100 patients with psychopathic personality are presented in table 1. All electroencephalographic patterns not

TABLE 1—*Incidence of Electroencephalographic Patterns with Relation to Primary Behavior Disorders and Psychopathic Personality*

Category *	Primary Behavior Disorders	Number or per Cent	Total Incidence of Abnormal Patterns
N		37	
QN		7	
RA		31	
CA		11	
P		14	
Total		100	56
	Psychopathic Personality		
N		42	
S <sub>1</sub>		43	
F <sub>1</sub>		3	
S <sub>2</sub>		9	
F <sub>2</sub>		1	
P		2	
Total		100	58

\* In accordance with both the electroencephalographic classification for children described under "method" and the classification for adults of Gibbs, Gibbs and Lennox,<sup>6</sup> N indicates a normal, QN, a questionably normal, RA, a recurrently abnormal, CA, a continuously abnormal, and P, a paroxysmal electroencephalographic pattern. S<sub>1</sub> indicates moderate amount of activity slower than 8½ cycles per second in any lead, F<sub>1</sub>, moderate amount of activity faster than 12 cycles per second in any lead, S<sub>2</sub>, great amount of activity slower than 8½ cycles per second in any lead, and F<sub>2</sub>, great amount of activity faster than 12 cycles per second in any lead.

considered as normal or questionably normal were designated as abnormal and for statistical purposes were treated as one category. Although the classificatory scales differ for the two diagnostic groups and the results can be compared directly only in part, the percentages of abnormality, 56 and 58, respectively, were very similar. These percentages are considerably higher than those reported for presumably normal children and adults. For a group of 270 unscreened children on whom records were made by one of us (J R K) the percentage of abnormality was approximately one-quarter the value of that for

6 Gibbs, F A, Gibbs, E L, and Lennox, W G. Electroencephalographic Classification of Epileptic Patients and Control Subjects, Arch Neurol & Psychiat 50 111-128 (Aug) 1943

the group of problem children. The most comprehensive electroencephalographic study of normal children has been made by Henry.<sup>7</sup> Through a personal communication, he indicated that his percentage of abnormal records was approximately one half of ours when essentially the same classification was used. Since the classificatory scale used for adults is the one described by Gibbs, Gibbs and Lennox,<sup>8</sup> comparisons may be made with the data obtained by these authors on neurologically screened subjects. For 1,000 of these subjects they reported an incidence of 15.8 per cent abnormal electroencephalograms. This is approximately one-fourth the occurrence of abnormality in our material.

One difference in the electroencephalographic abnormalities between patients with primary behavior disorders and patients with psychopathic personality is presented in table 1. There were 14 patients with primary behavior disorders who had paroxysmally abnormal electroencephalograms, whereas only 2 of the patients with psychopathic personality had similar electrocortical potentials. This difference has considerable meaning in terms of probabilities. Whereas a control normal adult population has an incidence of 0.9 per cent of paroxysmal waves, an epileptic population has at least 30 per cent.<sup>9</sup> Thus, a paroxysmally abnormal electroencephalogram would seem to indicate a high relationship to epilepsy. The inference seems clear that in spite of an attempt to eliminate all patients with epilepsy the younger group may contain patients who do not as yet show specific symptoms but who are potentially epileptic. The adult group may contain fewer such patients, since the aging process would assist in selectively preventing patients from being included in this group.

Although the distribution of the electroencephalographic patterns for patients with primary behavior disorders may suggest the inclusion of a small number who are potentially epileptic, the majority cannot be thought of as belonging to that clinical category. The high incidence of abnormal electroencephalograms for patients in the two diagnostic groups suggests that the cause of this abnormality must be sought elsewhere. So far as is known, permanent or relatively long-lasting electroencephalographic activity outside normal limits has been ascribed only to factors of inheritance, injury or infection of the brain and disturbances of cerebral metabolism. It, therefore, becomes pertinent to examine the historical material in terms of a positive family history and antecedent severe illness or cerebral injury to ascertain (1) the incidence of these factors with relation to the two conditions and (2) their relation to the abnormal electroencephalogram.

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<sup>7</sup> Henry, C. E. *Electroencephalograms of Normal Children*, Monographs of the Society for Research in Child Development, Washington, D. C., National Research Council, 1944, vol. 9, no. 3, 1-71.



First, the incidence of the components both of a positive family history and of a personal history of severe illness or cerebral injury may be considered. The data are presented in table 2. The components, or factors, for a positive family history are epilepsy, maladjusted personality, alcoholism and psychosis. In the analysis, both direct and collateral lines were included. The components, or factors, for illness or injury are anoxia, convulsions, head injury, severe illness, birth injury and prematurity. Irrespective of the number of times any one factor occurred in a patient's history, it was recorded but once. When two or more factors occurred, they were so recorded. Thus, there was a total of 80 factors in the family histories for 50 patients with

TABLE 2—*Incidence of the Components or Factors of Positive Family History, Antecedent Severe Illness and Cerebral Injury Among Patients with Primary Behavior Disorders or Psychopathic Personality*

	Primary Behavior Disorders		Psychopathic Personality		Totals	
	No of Patients	No of Factors	No of Patients	No of Factors	No of Patients	No of Factors
Family history						
Epilepsy		8		5		13 ( 6.5%)
Maladjusted personality		33		37		70 (35.0%)
Alcoholism		19		21		40 (20.0%)
Psychosis		20		23		43 (21.5%)
Totals	50	80	59	86	109 (54.5%)	
Illness or injury						
Anoxia		0		2		2 ( 1.0%)
Convulsions		10		4		14 ( 7.0%)
Head injury		10		10		20 (10.0%)
Severe illness		38		15		53 (26.5%)
Birth injury		19		5		24 (12.0%)
Prematurity		5		2		7 ( 3.5%)
Totals	55	82	31	38	86 (43.0%)	

primary behavior disorders and a total of 86 factors for 59 patients with psychopathic personality. In other words, some of the family histories, as well as some of the personal histories of illness or injury, contained two or more factors. There were 8 patients with primary behavior disorders and 5 patients with psychopathic personality who had epileptic relatives. When the two diagnostic groups were combined the percentage of patients with epileptic relatives was 6.5. The incidences of maladjusted personality, alcoholism and psychosis in the family histories were remarkably similar for the two diagnostic groups (33, 19 and 20 and 37, 21 and 23 per cent respectively). Thus, the incidence of a family history of maladjusted personality was about twice that of alcoholism and psychosis and about four times that of epilepsy.

The higher incidence of factors of illness and injury in the group with primary behavior disorders is quite evident on examination of the lower half of the table. There was a total of 82 factors of illness or injury for 55 patients with primary behavior disorders, in contrast

to a total of 38 factors for 31 patients with psychopathic personality. The incidences of severe illness, questionable birth injury and convulsions were considerably greater for the younger than for the older population (38, 19 and 10 and 15, 5 and 4 per cent, respectively) The incidences of head injury were the same for the two groups (10 per cent each) This greater incidence of illness and injury for the patients with primary behavior disorders suggests that there may be included within this group a larger number of patients whose adjustment is related to these factors<sup>8</sup> than is to be found among the psychopathic personalities

TABLE 3—*Analysis of the Electroencephalogram with Relation to Antecedent Severe Illness and/or Head Injury and Positive Family History*

	Electroencephalograms							
	Abnormal		Questionably Normal		Normal		Total Incidence	
	No	%	No	%	No	%	No	%
<b>Primary Behavior Disorders</b>								
Positive family history only	14	56	5	20	6	24	25	25
Previous illness and/or injury only	19	63			11	37	30	30
Positive family history and previous illness and/or injury	15	60	1	4	9	36	25	25
No positive family history or previous illness or injury	8	40	1	5	11	55	20	20
Totals	56	56	7	7	37	37	100	100
<b>Psychopathic Personality</b>								
Positive family history only	29	65			16	35	45	45
Previous illness and/or injury	10	59			7	41	17	17
Positive family history and previous illness and/or injury	11	79			3	22	14	14
No positive family history or previous illness or injury	8	33			16	67	24	24
Totals	58	53			42	42	100	100
<b>Both Conditions</b>								
Positive family history only	43	62	5	7	22	31	70	35
Previous illness and/or injury only	29	62			18	38	47	23.5
Positive family history and previous illness and/or injury	26	67	1	2	12	31	39	18.5
No positive family history or previous illness or injury	16	36.5	1	2.5	27	62	44	22
Totals	114	57	7	3.5	79	39.5	200	100

Second, an analysis of the relation of the electroencephalographic patterns to the categories of positive family history and previous severe illness or cerebral injury in the two groups of patients may now be considered. The data are presented in table 3. The first part presents the data for patients with primary behavior disorders, the second, for

<sup>8</sup> The difference in the incidence of illness and injury may be related to the historical method. The younger the patient, the more likely is a severe illness or injury to be recalled by relatives and reported by them. Because of this tendency, further critical comparisons are indicated, which will be discussed in a subsequent publication.

patients with psychopathic personality, and the third for a combination of the two. The incidence of the factors of positive family history and previous illness and injury was classified under four categories: (1) positive family history only, (2) previous severe illness and/or cerebral injury only, (3) positive family history and previous severe illness and/or cerebral injury, and (4) absence of positive family history or previous severe illness or cerebral injury. The incidence of these categories for the two groups of patients may be compared. When the categories of positive family history only and positive family history and previous illness and/or injury were combined for the two groups of patients, the total incidence of positive family history became 50 per cent for primary behavior disorders and 59 per cent for psychopathic personality. A similar comparison may be made for the incidence of previous illness and/or injury. When the two categories of previous illness and/or injury only and positive family history and previous illness and/or injury were combined, the incidence of previous illness and/or injury was 55 per cent for primary behavior disorders and 31 per cent for psychopathic personality. Again, this indicates the greater incidence of illness and/or injury in the patients of the former group.

The relation of the electroencephalogram to the categories for the two groups of patients, single and combined, may now be considered.

In the group of primary behavior disorders, 14 children with positive family history only had abnormal electroencephalograms, and 6 had normal records. Eight children with negative family and personal histories had abnormal electroencephalograms, and 11 had normal records. By subjecting these two distributions to the chi square test ( $\chi^2$ )<sup>9</sup> for independence, it was found that a level of significance of 5 to 10 per cent was obtained. This means that the two distributions would be expected to differ from 5 to 10 times in 100 series of observations. Hence, this difference may be regarded as marginally significant.

Nineteen children giving a positive personal history of illness and/or injury showed abnormal electroencephalograms, and 11 had normal records. When this distribution is compared with that for the group with negative family and personal histories, a level of significance of 10 to 20 per cent is obtained. This is not sufficiently great to suggest that the two groups differ significantly.

When the 15 children with abnormal electroencephalograms who presented both a positive family history and a personal history of illness and/or injury and the 9 children with normal records but with similar histories were compared with the group with negative family and personal histories the level of significance obtained was

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<sup>9</sup> Lindquist, E. F. *Statistical Analysis in Educational Research*, New York, Houghton Mifflin Company, 1940, p. 41.

from 10 to 20 per cent. These two groups, therefore, did not differ more than may be accountable by chance.

In contrast, for the patients with psychopathic personality, the distributions of all three of the categories with positive factors were significantly different from the distribution of the category without positive factors. The levels of significance, as revealed by the  $\chi^2$  test, were between 1 and 2 per cent.

When the group of patients with psychopathic personality and that with primary behavior disorders were combined, the distributions of all three of the categories with positive factors were significantly different from the distribution of the category without positive factors. The levels of significance, as revealed by the  $\chi^2$  test, were then between 1 and 2 per cent. This combination of groups appeared justified in view of the fact that a statistical comparison of each subgroup (positive family history, positive personal history, combined positive family and personal histories, and negative history) for the patients with primary behavior disorders and psychopathic personality yielded levels of significance which made it unnecessary to reject the hypothesis that the compared distributions did not suffer.

Thus, these data strongly indicate that the abnormal electroencephalograms are related both to the selected factors in the family history and to severe illness and/or cerebral injury sustained early in life. The lack of significance in the difference between the categories containing illness and/or injury and the category without any positive factors for the patients with primary behavior disorders may be due to either or both of two factors: (1) the high percentage of abnormal electroencephalograms in the category without positive factors, and/or (2) the selective effect of illness or injury on the abnormality of the electroencephalogram.

Since there seems to be a relation between electroencephalographic abnormality and either positive family history or previous severe illness and/or cerebral injury or both, further problems appear. Are certain of the selected criteria for a positive family history or for the personal history of illness or injury of the patient closely related to electroencephalographic abnormality, and are certain others not? The data pertaining to the first part of this question may now be considered. Table 4 presents a summary of the electroencephalographic data in relation to the four selected components of the category of positive family history only: epilepsy, maladjusted personality, chronic alcoholism and psychosis. The category of positive family history and previous illness and/or injury was omitted so that the complications from illness and injury would be minimized. There were 70 patients—25 with primary behavior disorders and 45 with psychopathic personality. Some patients had two or more components in their family history; thus

TABLE 4—Analysis of the Electroencephalogram with Relation to Factors of the Category of Postive Family History Only

Family History	Primary Behavior Disorders			Psychopathic Personality			Totals		
	Abr *	QN	N	Totals	Abn	N	Totals	Abn	Totals
Epilepsy	3	0	0	3	2	0	2	5 (100%)	5 (100%)
Maladjusted personality	8	4	4	16	19	9	28	27 (61.8%)	44 (100%)
Alcoholism	5	2	3	10	9	8	17	14 (51.9%)	27 (100%)
Psychosis	4	3	2	9	6	10	16	10 (40%)	25 (100%)
No positive family history or previous illness and/or injury	8 (40%)	1 (5%)	11 (55%)	20 (100%)	8 (33.3%)	16 (66.7%)	24 (100%)	16 (36.5%)	44 (100%)

\* In this table and in tables 5 and 6, Abn indicates abnormal, QN, questionable normal, and N, normal electroencephalograms

the total number of components will be more than the number of patients involved

Although there were but 5 patients with a family history of epilepsy, it was of interest to note that the patients coming from those families had abnormal electroencephalograms

The component that occurred most frequently in the family histories of these patients was maladjusted personality. There were 44 families which contained one or more members so classified. Twenty-seven of these members, or 61.3 per cent, had abnormal electroencephalograms. When the distribution of this group was compared with the distribution of the group without any positive factors by the method of  $\chi^2$ , a level of confidence of 1 per cent was found. This means that the difference in the two distributions could be attributed to chance in only 1 out of 100 experiments and is thus statistically significant.

There were 27 patients whose family history was characterized by one or more members being judged as chronically alcoholic. Fourteen patients, or 51.9 per cent, had abnormal electroencephalograms. There were 25 patients whose family history was characterized by one or more members being or having been psychotic. Ten patients, or 40 per cent, had abnormal electroencephalograms. When the distribution of either of these two groups, patients with a family history of chronic alcoholism and patients with a family history of psychosis, were compared by the  $\chi^2$  test with the distribution for the group without any positive factors in the family history, the difference was found to be statistically insignificant.

These data, then, suggest that two groups of patients, those in whose family history there were epilepsy and maladjusted personality, respectively, were characterized by a significantly greater proportion of electroencephalographic abnormality than the group with a negative family and personal history. In contrast, the other two groups, patients with a family history of chronic alcoholism and psychosis, were not so characterized.

Since the groups with the family histories of maladjusted personality and chronic alcoholism were logically so similar, yet differed in their comparison with the group with a negative history, they were themselves compared with the  $\chi^2$  test. The level of significance attained was definitely insufficient to warrant rejecting the hypothesis that they differed except by chance.

Inasmuch as alcoholism, in the present histories, occurred predominantly in the male parent, and maladjusted personality occurred almost equally in the male and in the female parents, it seemed possible to assess the relationship between the sex of the parent and the abnormality of the patient's electroencephalogram. Of the 44 patients with a positive family history only, with one or more relatives considered as

having maladjusted personality, the father was the closest relative of 15, and the mother, of 17. Of the patients whose fathers were considered as maladjusted, 6 (40 per cent) had abnormal electroencephalograms, while of the patients whose mothers were so considered 13 (76 per cent) had abnormal electroencephalograms. The  $\chi^2$  test revealed a level of significance between 2 and 5 per cent. The sex of the parent thus seems related to the abnormality of the patient's electroencephalogram.

Of the 27 patients with one or more relatives who were considered alcoholic, the father was the closest relative of 16, and the mother, of 1. Seven (44 per cent) of the patients whose fathers were judged to be alcoholic had abnormal electroencephalograms. This number was approximately the same as that of patients with abnormal electroencephalograms whose fathers were judged as maladjusted. There were 3 patients both of whose parents were considered maladjusted and 1 patient both of whose parents were considered alcoholic. All 4 patients had abnormal electroencephalograms, thus suggesting that when both parents were involved there was a greater probability of abnormal electrocortical activity in the patient. These patients were too few for statistical analysis.

Further evidence of these relations may be obtained by analyzing the category of patients with positive family history and previous illness and/or injury. Of the 10 patients whose fathers were considered to have maladjusted personality, 5 (50 per cent) had abnormal electroencephalograms. Of the 10 patients whose fathers were considered alcoholic, 6 (60 per cent) had abnormal electrocortical potentials. Of the 6 patients whose mothers were considered to have maladjusted personalities, 4 (66.7 per cent) had abnormal electroencephalograms. There were no patients in this category whose mothers were judged alcoholic. There were 3 patients both of whose parents were considered maladjusted. Two (66.7 per cent) of these had abnormal electroencephalograms. While there were few cases for analysis, the trend for this category was similar to the trend for the category of patients with positive family history only.

When these categories are combined and the patients whose relatives had either maladjusted personality or chronic alcoholism are considered as one group, the data may be summarized as follows. Of 51 patients whose fathers were considered either as having maladjusted personality or chronic alcoholism, 24, or 47 per cent, had abnormal electroencephalograms. Of 24 patients whose mothers were considered to have a similar condition, 17, or 70.8 per cent, had abnormal electrocortical potentials. The  $\chi^2$  test revealed a level of significance of 5 to 7 per cent. Of 7 patients with both parents similarly classified, 6, or 85.7 per cent, had abnormal waves. It would thus seem that the incidence of abnormal electroencephalograms would be greater not only

for those patients whose mothers, in contrast to the fathers, were judged maladjusted but that it would be still greater for those patients both of whose parents were so judged. This is strongly suggestive of a relationship between sex of the parent and abnormality in the patient.

The data presented in table 3 indicated that the abnormal electroencephalograms of the patients with psychopathic personality and primary behavior disorders when combined were related to the factors in both the family history and the personal history. To be considered now is the relation of the patients' electroencephalograms to the factors of previous severe illness and cerebral injury. Table 5 presents such a relationship\* in the category of severe illness and/or cerebral injury only. By considering this category alone, the complication of factors of a positive family history is reduced. The six selected factors in the personal history were anoxia, convulsions, head injury, severe illness, questionable birth injury and prematurity. There were 30 patients with primary behavior disorders who had personal histories which included a total of 47 of these selected factors. There were 17 patients with psychopathic personality who had histories which included a total of 19 factors. Thus, some of the patients had a history of more than one of these factors.

The incidence of a history of convulsions, severe illness and questionable birth injury was greater for patients with primary behavior disorders than for those with psychopathic personality. The numbers for each factor, however, were too small to allow statistical comparisons.

There were 7 patients with a history of convulsions, 5, or 71.4 per cent, had abnormal electroencephalograms. There were 9 patients with a history of head injury, 6, or 66.7 per cent, had electroencephalographic abnormality, of which 3 showed signs of localization. There were 33 patients with a history of severe illness, 21, or 63.6 per cent, had abnormal electrocortical potentials. When the distribution of this last group was compared with the distribution of the category with no positive factors by the  $\chi^2$  test, a level of significance of 2 per cent was obtained. There were 14 patients with a history of questionable birth injury, 7, or 50 per cent, had abnormal electroencephalograms. When the distribution of this group was compared with the distribution of the category with no positive factors by the  $\chi^2$  test, a level of significance of 50 to 70 per cent was obtained. The first statistical comparison may be regarded as strongly suggesting that the two distributions differ, while the second does not.

The largest group, that of 33 patients with previous severe illness, lent itself to further analysis. Table 6 presents an analysis of the electroencephalographic data with reference to the degree of severity and the age of occurrence of the illness for both the category of severe illness only and that of positive family history and severe illness. In the category of severe illness alone only 30 patients could



TABLE 5—Analysis of the Electroencephalogram with Relation to the Factors of the Category of Severe Illness and/or Cerebral Injury Only

Illness or Injury	Primary Behavior Disorders			Psychopathic Personality			Totals		
	Abn	QN	N	Abn	N	Totals	Abn	QN	N
Anoxia	0	0	0	0	0	0	0	0	0
Convulsions	4	0	2	1	0	1	5 (71 4%)	0	2 (23 6%)
Head injury	3	0	2	3	1	4	6 (66 7%)	0	3 (33 3%)
Severe illness	15	0	8	6	4	10	21 (63 0%)	0	12 (36 4%)
Birth injury	5	0	6	2	1	3	7 (50 0%)	0	7 (50 0%)
Prematurity	1	0	1	0	1	1	1 (33 3%)	0	2 (66 7%)
No positive family history or previous illness and/or injury	8 (40 0%)	1 (5 0%)	11 (55 0%)	8 (33 3%)	16 (66 7%)	24 (100%)	16 (36 5%)	1 (2 5%)	27 (62 0%)
Totals			20 (100%)						44 (100%)

TABLE 6—Analysis of the Electroencephalogram with Relation to the Degree of Severity\* and Age of Occurrence of Illness

Degree of Severity	1 to 3 Years			4 to 6 Years			7 Years			Totals		
	Abn	N	Totals	Abn	QN	N	Abn	N	Totals	Abn	QN	N
Severe illness only	5	0	5	1	0	0	1	0	1	7 (100%)	0	0
	++	7	2	3	0	5	1	5	6	11 (47 8%)	0	12 (52 2%)
				4	0	5	2	5	7	18 (60 0%)	0	12 (40 0%)
Totals		12	2									
Positive family history and severe illness	3	0	3	1	0	2	0	0	0	4 (66 7%)	0	2 (33 3%)
	++	3	3	2	1	1	3	1	4	8 (67 1%)	1 (7 2%)	5 (35 7%)
Totals	6	3	9	3	1	3	3	1	4	12 (60 0%)	1 (5 0%)	7 (35 0%)
Totals	8	0	8	2	0	2	1	0	1	11 (84 6%)	0	2 (15 4%)
	++	10	5	5	1	6	4	6	10	19 (51 3%)	1 (2 8%)	17 (45 9%)
Totals		18 (78 3%)	5 (21 7%)	7 (41 2%)	1 (3 8%)	8 (50 0%)	5 (45 5%)	6 (54 5%)	11	30 (60 0%)	1 (2 0%)	19 (38 0%)

\* Very severe illness is indicated by ++++ moderately severe illness by ++

be used, for the age at which the other 3 patients were ill was not known. The degree of severity was subdivided into the very severe (+ + + +) and the moderately severe (+ +). There were 7 patients with very severe illnesses. Four had prolonged elevation of temperature, signs of meningeal irritation and coma, followed by a history of temporary regression in development, 2 had prolonged high temperatures with prolonged delirium or coma, and 1 had a severe attack of pertussis at the age of 6 months. The moderately severe illnesses were all characterized by high temperatures and stupor or delirium but no meningeal irritation or history of subsequent regression in development. All patients who had very severe illnesses only had abnormal electroencephalograms. Eleven of the 23 patients with histories of moderately severe illness only had abnormal electroencephalograms.

In the other category, that of positive family history and severe illness, there were 6 patients with a history of very severe illness, 4 (66.7 per cent) of whom had abnormal electroencephalograms, and 14 patients with moderately severe illness, 8 (57.1 per cent) of whom had abnormal electroencephalograms. The consistency of the data for these two categories, then, would seem to indicate that severity of illness is related to the development of an abnormal electroencephalogram.

When the distribution for very severe illness, regardless of family history, was compared with the distribution for moderately severe illness, regardless of family history, by means of the  $\chi^2$  test, the level of significance was between 2 and 5 per cent.

Further examination of the table indicates that the age at which the illness occurred seems to bear some relationship to the electrical activity of the brain. It may be noted that, irrespective of the degree of severity of the illness, the younger the patient at the time of the illness the greater the probability of his having an abnormal electroencephalogram. Of those patients whose illnesses occurred within the first three years of life, 78.3 per cent had abnormal electroencephalograms. For those whose illnesses occurred after that time, only 44.4 per cent had a similar abnormality. Although the data are not presented, the type of illness, such as pneumonia, pertussis, measles and fevers of unknown origin, seemed to show no relation to the type of the electroencephalogram, neither did the time interval between the occurrence of the illness and the electroencephalographic recording. Thus, two factors seemed to be operating, more or less independently, in association with a severe illness to produce long-lasting disturbance in the electrical activity of the brain: the degree of severity of the illness and the age at which the illness occurred.

#### COMMENT

The diagnoses of primary behavior disorders and psychopathic personality refer primarily to the personality structure and the behavior on

a descriptive basis rather than to any constellation of factors important in causation of the disturbances. They are descriptive diagnoses which most probably include a number of clinical conditions. The data presented in this report suggested this. The two diagnostic groups in this study were characterized by a high incidence of electroencephalographic abnormality. The higher incidence of paroxysmal electroencephalograms in the patients with primary behavior disorders than that in the patients with psychopathic personality would imply that more patients with preclinical epilepsy were included in the former than in the latter group. It is to be expected that the latter group would contain fewer such patients, for they were older and age acted as a selective factor. Moreover, the greater incidence of severe illness or cerebral injury sustained early in life in the younger group than in the older one would suggest these factors, too, as possibly etiologic. Thus, within the large descriptive diagnostic groups there may be, on the basis of the data presented, smaller, more specific etiologic subgroups.

The data strongly suggest that abnormal electroencephalograms were obtained for a higher percentage of patients who had either a positive family history or a personal history of antecedent severe illness or cerebral injury than for those patients for whom neither factor appeared. In the family history, the factors of maladjusted personality and epilepsy appeared of greater importance than the factor of psychosis. The designation of "alcoholism" really included disturbance in personality function. When the histories were analyzed to discover whether the male or female parent showed maladjustment or alcoholism, it was found that there was a higher incidence of abnormal electroencephalograms among the patients whose mothers were evaluated as maladjusted or alcoholic than in those patients whose fathers were so judged. This relationship is consistent with the data reported by Lennox, Gibbs and Gibbs<sup>10</sup> on the inheritance of cerebral dysrhythmia and epilepsy. Their data, too, suggested the possibility that females carry a greater inheritance factor, as expressed by dysrhythmia and by family history, than that carried by males. As in their data, so in ours, there is no suggestion of sex linkage in the occurrence of dysrhythmia.

Lennox, Gibbs and Gibbs<sup>10</sup> stated that approximately 60 per cent of the near relatives of epileptic patients had abnormal electrocortical activity. However, only 24 per cent (parents, siblings and children) had a history of seizures. Thus, persons with abnormal electroencephalograms outnumber persons with seizures in a ratio of 25:1. Since the incidence of epilepsy in the population is 0.5 per cent, they concluded

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10 Lennox, W. G., Gibbs, E. L., and Gibbs, F. A. Inheritance of Cerebral Dysrhythmia and Epilepsy, *Arch Neurol & Psychiat* **44** 1155-1183 (Dec.) 1940

that approximately 12 per cent of the population have an abnormal electroencephalogram—"about 15,000,000 in the United States"—a statement supported by random electroencephalographic sampling of the population. The samples reported here of the population with psychopathic personality and primary behavior disorders were characterized by high incidences (58 and 56 per cent, respectively) of abnormal electroencephalographic activity. It is well known that many relatives of epileptic patients who do not have epileptic manifestations reveal unusual behavior patterns. One may therefore ask: What is the relation of the populations under study here to the seizure-free relatives of epileptic patients? What is the relation of these populations to the 15,000,000 persons in the United States with cerebral dysrhythmia?

Although the data would indicate a relation of the abnormal electroencephalogram to psychopathic personality or primary behavior disorders, it must not be considered pathognomonic for either. This is obvious from the electroencephalographic examination of any psychiatric or neurologic population. In fact, Liberson and Segun<sup>11</sup> have indicated a relation between a positive family history and abnormal electrocortical activity for a number of psychiatric conditions, with the inference of inheritance of the abnormal waves. Moreover, there are persons generally conceded to be "normal" who show electroencephalographic characteristics falling beyond the present concept of normality. This is of common electroencephalographic experience. It has been reported<sup>10</sup> for relatives of patients with epilepsy, and it is known to be true for relatives of patients with either psychopathic personality or primary behavior disorders.<sup>12</sup> Abnormality of the electroencephalogram is not necessarily indicative of abnormality in behavior; it is merely indicative of an apparently reliable probability that there may be some kind of behavioral deviation sooner or later. This may account for the relatively high percentage of abnormal electroencephalographic activity in the group of patients without either a positive family history or a personal history of severe illness or cerebral injury sustained early in life.

This relatively high percentage of abnormal electroencephalograms in the group of patients without any positive abnormality in the family history or personal history of illness or injury for both primary behavior disorders and psychopathic personality is most probably inherited.<sup>12</sup> This probability must be kept in the foreground when considering the factors of severe illness and cerebral injury. An evaluation of any

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11 Liberson, W. T., and Segun, C. A. Brain Waves and Heredity in Mental Diseases, *Psychosom Med* 7 35-38 (Jan) 1945

12 Unpublished data on the relationship of the electroencephalograms of the parents to those of the patients

experience of the latter kind is complicated by its possible superimposition on the inherited characteristics of the patient populations. Nevertheless the patients who had personal histories of convulsions, head injury with unconsciousness or severe illness showed a higher incidence of abnormal electrical activity of the brain than the patients with no such experiences. Factors of severe illness which were of importance were the degree of severity and the age at which the illness occurred. The more severe the illness and the younger the patient at the time of its occurrence, the greater the probability of an abnormal electroencephalogram. This was true irrespective of the type of the severe illness. Heppenstall and Hill<sup>13</sup> have likewise shown that patients under 20 years of age at the time of a head injury had a greater probability of abnormal electrocortical activity than those who were older. A higher incidence of abnormal electrocortical activity in patients having a history of convulsions during early life is to be expected. The probability of their relation to epilepsy is greater than that due to chance.

The implications of an abnormal electroencephalogram are clear—that there probably is some pathophysiologic process in the cortex. The implications of a normal record are equally clear—that there probably is no pathophysiologic process in the cortex. These implications must be considered in terms of the theory of probability, for it is known that such a process may be dormant at the time of recording, and thus not be made apparent on the record. Furthermore, assumptions of the presence or absence of a pathophysiologic process can at present be referred only to the cortex. Subcortical processes may not be normal, yet the electroencephalogram may be repeatedly without discernible abnormal activity.

The electroencephalographic data, therefore, would indicate that there is a high incidence of discoverable and repeatedly verifiable abnormal organic processes in the heterogeneous group of disturbances diagnostically categorized, respectively, as primary behavior disorders and psychopathic personality. These abnormal processes would appear to be inherited. Furthermore, pathophysiologic experiences, either chemogenic or histogenic, if either early enough or severe enough, would likewise lead to the development of abnormal processes. May not the inference be made that these abnormal processes are related to the maladjustment of the patients, that they may indicate the organism's susceptibility to difficulties in behavioral adjustment, that persons with such abnormal processes may possess less elasticity in their neural limits for withstanding the stresses and strains of the adjustment process?

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13 Heppenstall, M. E., and Hill, D. Electroencephalography in Chronic Post-Traumatic Syndromes, *Lancet* 1 261-263 (Feb 27) 1943

that their response tendencies have been altered and that they have poorer adaptation in their interreaction with the social environment?

These abnormal organic processes should not be considered the sole etiologic factor for the behavioral disturbances of the patients. Etiology from a psychiatric viewpoint always involves a constellation of factors, genogenic, histogenic, chemogenic and psychogenic, with their relative interrelationships. The presence of an abnormal electroencephalogram would add weight to genogenic, histogenic and chemogenic factors, which otherwise might be undervaluated. The majority of the abnormal electroencephalograms would appear to be genogenic, a minority would appear to be physiogenic (histogenic or chemogenic), for normal electroencephalograms no inferences as to disturbed pathophysiologic cortical processes could be made, although such may be present. The electroencephalogram cannot, of course, indicate the totality of the etiologic constellation, although it may assist in the more adequate evaluation of the etiologic factors in a given patient's disturbance—ancestral transmission, physical trauma and social or emotional trauma.

#### SUMMARY

- 1 Two hundred patients, 100 each with primary behavior disorders and with psychopathic personality, showed considerably higher percentages of electrocortical abnormality, 56 and 58 per cent, respectively, than the percentages reported for presumably neurologically normal children and adults.

- 2 Fourteen per cent of the patients with primary behavior disorders, in contrast to 2 per cent of the patients with psychopathic personality, had paroxysmal electroencephalographic activity.

- 3 The incidences in the family history of epilepsy, maladjusted personality, chronic alcoholism and psychosis were similar in the two diagnostic groups.

- 4 The incidences in the personal history of convulsions, severe illness and questionable birth injury were greater for the group of patients with primary behavior disorders than for the group with psychopathic personality. The incidences of head injury were similar for the two groups.

- 5 When the two groups of patients were combined, significantly greater proportions of abnormal electroencephalograms were found when there was a family history either of epilepsy or of maladjusted personality.

- 6 The proportion of patients showing electroencephalographic abnormality appeared to be greater when the mothers were judged maladjusted or alcoholic than when the fathers were so judged.

7 When the two groups of patients were combined, significantly greater proportions of abnormal electroencephalograms were found when there was a personal history of convulsions, head injury with unconsciousness or severe illness

8 For the category of severe illness, the younger the patient at the time of the illness and/or the more severe the illness, the greater the probability of abnormal electrocortical activity

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## CLEIDOCRANIAL DYSOSTOSIS WITH PSYCHOSIS

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THERE was recently admitted to and treated at Duke Hospital a patient with cleidocranial dysostosis and a psychosis. The case was of especial interest because of the concatenation of the rare anatomic anomaly and schizophrenia. Particularly noteworthy in this case was the absence of psychotic manifestations in the patient's father, who possessed essentially the same physical defects to an even greater degree. The rarity of cleidocranial dysostosis, the constancy of the physical manifestations of the syndrome and the autosomal mendelian dominant mode of inheritance of the trait in at least the majority of instances<sup>1</sup> make it worth while to redescribe this condition and to report an additional case even if it were not for the unusual psychiatric implications.

Cleidocranial dysostosis is a rare syndrome, affecting persons of both sexes and of all ages, and occurs in diverse racial and national groups. In 1760 Meckel<sup>2</sup> reported the case of an infant born without clavicles, and in 1765 Martin<sup>3</sup> gave details of a family several members of which had abnormal clavicles. In 1897 Marie and Santon<sup>4</sup> described the association of clavicular and cranial defects in members of two families, and the following year they proposed the name *dysostose cléido-crânienne héréditaire*<sup>5</sup>. In a monograph Hultkrantz<sup>6</sup> discussed

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1 Lasker, G W. The Inheritance of Cleidocranial Dysostosis, Human Biol, to be published

2 Meckel. Mém de Paris, 1760, cited by Terry, R J. Rudimentary Clavicles and Other Abnormalities of the Skeleton of a White Woman, J Anat & Physiol **33** 413-422, 1899

3 Martin. Sur un déplacement naturel de la clavicule, J de med, chir, pharm **23** 456-460, 1765

4 Marie, P, and Santon, P. Observation d'hydrocéphalie héréditaire (père et fils) par vice de développement du crâne et du cerveau, Bull et mém Soc med d hôp de Paris **14** 706-712, 1897

5 Marie, P and Santon, P. La dysostose cléido-crânienne héréditaire (hydrocéphalie héréditaire), Bull et mém Soc med d hôp de Paris **15** 436-437, 1898

6 Hultkrantz, J W. Ueber Dysostosis cleido-cranialis kongenitale kombinierte Schädels- und Schlüsselbeinanomalien Ztschr f Morphol u Anthropol **11** 385-528, 1908



all the material available in 1908, and this publication remains one of the most thorough treatises on the subject. A good general description in English is provided by Eldridge, Simon and Ramos,<sup>7</sup> and a modern review is given by Carriere and associates.<sup>8</sup> In 1929 Fitchet<sup>9</sup> published an excellent review, with a bibliography of over 125 items and with abstracts of most of the cases. Engel,<sup>10</sup> in a systematic study of the syndrome, summarized 228 cases and noted that 87 additional cases were said to have occurred in the families of the affected patients. We have used some of Engel's statistics on cases published up to 1933, inclusive, in compiling our summaries. Since 1933, 145 new cases have been reported and an additional 63 cases mentioned. Altogether, there have been approximately 275 publications on the subject, of which 245 have been reviewed by one of us (G W L).<sup>11</sup> However, the infrequency of the condition is attested to by the fact that only 1 previous case of cleidocranial dysostosis appears in the records of the quarter of a million patients seen at Duke Hospital since its opening, fifteen years ago.<sup>12</sup>

In a typical case of cleidocranial dysostosis the head is large, especially in comparison with the face, and it is wide and flat, with protruding cranial bosses and bulging frontal region. The bones of the cranial vault are slow to develop, so that the fontanels and sutures are widely separated at birth and may remain apart into adulthood. Usually there is a depression at the fontanels, and sometimes a pulse may be felt there if the bone is absent. There are furrows along the lines of the sutures, which mark thinning or separation of the bones. The bosses, however, are much thickened. One of the most conspicuous clinical signs is a sagittal groove dividing the forehead and marking the frontal suture, which regularly persists in cases of this anomaly. Many wormian bones occur in the sutures, and extra sutures have been observed dividing the parietal bones (horizontally) and the malar bones and occurring elsewhere. The frontal sinuses have been reported

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7 Eldridge, W W, Simon, A, and Ramos, R. Cleidocranial Dysostosis. A Case Report, *Am J Roentgenol* **34** 41-49, 1935.

8 Carriere, G, Huriez, C, and Decamps, G. La dysostose cleidocrânienne (maladie de Pierre Marie et Santon), *Gaz d hop* **110** 701-707, 733-741 and 765, 1937.

9 Fitchet, S M. Cleidocranial Dysostosis. Hereditary and Familial, *J Bone & Joint Surg* **11** 838-866, 1929.

10 Engel, E. Dysostosis Cleidocranialis, *Helvet med acta* **4** 158-174, 1937.

11 A complete bibliography will be found in conjunction with Lasker's article.<sup>1</sup>

12 Dr Angus McBryde has permitted us to examine the records, photographs and roentgenograms in a case of cleidocranial dysostosis in a 12 year old white boy, who had typical cranial and clavicular anomalies and pronounced pelvic changes, including a very wide pubic symphysis. This boy was of normal intelligence and the only child of normal parents.

to be absent or much reduced in 24 cases. Supraorbital ridges are frequently absent. The mastoids are often virtually lacking, a trait which has been explained as a result of absence of the clavicles and consequent maldevelopment of the sternocleidomastoid muscles. However, a case has been reported by Rhinehart<sup>13</sup> in which the mastoids were missing but the clavicles were normal. The base of the skull is frequently poorly developed (which may contribute to the brachycephaly), and platybasia, with downward bending of the occiput, is mentioned in some cases. The sella turcica was noticed to be large in 5 cases but was reported as normal in 16 other cases and as small in 2 cases.

The face is usually poorly developed. The bridge of the nose is cartilaginous, the nasal, and sometimes the lacrimal, bones being deficient or completely absent. The root of the nose is therefore regularly depressed, but it is often wide, so that a mongoloid fold may cover the inner canthus of the eye. Hypertelorism has been reported in 17 cases. The orbits are relatively high, but a tendency to exophthalmos is sometimes reported. The malar bones are small, and the zygomatic arch in some cases is incomplete. The palate is typically high-arched and narrow, and development may be defective, leaving a cleft. In 20 cases the high palate was lacking, but even in several of these the palate was narrow. The mandible, being usually prognathous, is frequently disproportionate to the rest of the face. This may be caused chiefly by maldevelopment of the cranial base and a correlated underdevelopment of the middle of the face. In several cases the mental symphysis has been reported to persist.

The dentition is usually conspicuously affected. The milk teeth appear later than is normal in infants but are usually not anomalous in other respects. They are not replaced at the proper time by the permanent teeth, and there is virtually never a full complement of teeth in the mouth of the adult, despite a tendency to supernumerary anterior teeth. Unerupted teeth are found in the mandible and maxilla in most cases, and eruption of teeth in older persons is frequently noted. Dentigerous cysts sometimes occur. The teeth are usually irregular in position, and the occlusion is so bad that many persons have their teeth extracted and wear dentures. Advanced dental caries is often reported. Enamel hypoplasia, malformed roots and enlargement or dwarfing of teeth are sometimes seen. Speech defects associated with the dental anomalies have been reported in 3 cases.

In the case reported by Russo-Frattasi<sup>14</sup> there was an abnormality of the right middle ear and of the tympanic membrane. In the case

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<sup>13</sup> Rhinehart, B. A. Cleidocranial Dysostosis (Mutational Dysostosis) with a Case Report, *Radiology* 26 741-748, 1936.

of Eldridge and others<sup>7</sup> there was a history of partial deafness for twenty-two years. Stahl's<sup>15</sup> patient was partially deaf, and 2 of the dysostotic members of the family studied by Miles<sup>16</sup> were deaf.

The dysostotic person is often very short. For 34 men for whom the stature was reported, the height averaged 156.6 cm and ranged from 132 to 178 cm. Among 34 adult women, the recorded heights ranged from 110 to 159 cm, with an average height of 144.6 cm. Medium statures are found occasionally and probably occur more frequently than is stated in the published reports. Altogether, 131 patients were described as small or slender, 32 as of average size and only 1 as large. In children, as in adults, dwarfing may be very common with this condition. In infants, however, the size is frequently normal, and the stunting becomes apparent only later.

The short stature is usually, at least in part, the result of abnormal curvatures of the vertebral column, kyphosis, lordosis or scoliosis being mentioned in about 55 cases. Scoliosis is the most frequent. Wedging of the vertebral bodies is common. Spina bifida occulta has been reported in 51 cases in which roentgenograms were made and often occurs in the cervical and upper dorsal regions (which is uncommon in the general population). At least 3 instances of cervical meningocele have been reported. The thorax is sometimes conical or funnel shaped and sometimes flattened from side to side. Many cases with a rachitic appearance of the thorax or ribs have been reported. The sternum was depressed in several cases, and the manubrium and the xiphoid process have been found lacking. Cervical ribs have been reported in 7 instances.

Defective clavicles constitute the most characteristic trait of cleidocranial dysostosis. One or both bones may be completely lacking (10 and 30 cases, respectively), but more frequently one or both are imperfect. Frequently there is a sternal bony rudiment, or even an only slightly shortened bone attached to the sternum. Occasionally there is also an acromial rudiment, which may be widely separated from the other fragment or may form a pseudoarthrodial joint. Especially when one only of the clavicles is divided (the right clavicle remained intact in 5 cases and the left in 27), the differential diagnosis of an ununited fracture may be of practical importance. One patient with a unilateral congenital clavicular defect is reported to have swindled thousands of

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14 Russo-Frattasi, G. Rara anomalia dell'orecchio medio in disostosi cleidocranica, *Oto-rino-laring ital* 4:484-502, 1934.

15 Stahl, F. C. Neue Beiträge zur Physiognomik und pathologischen Anatomie der Idiotia endemica (genannt Cretinismus), Erlangen, Ferdinand Enke, 1848, pp. 53-57.

16 Miles, P. W. Cleidocranial Dysostosis. Survey of Six New Cases and One Hundred and Twenty-Six from the Literature, *J. Kansas M. Soc.* 41:462-468, 1940.

dollars by feigning a fracture. Another practical problem arose in a case in which surgical removal of a clavicular fragment was required to relieve symptoms caused by pressure on the brachial plexus, and in a similar case a bone graft was employed to reunite the free ends of the clavicle.

In a few persons related to patients with the typical syndrome one finds clavicular anomalies but no alteration of the skull. The signs referable to the skull are therefore not necessarily always present with the dysostosis. On the other hand, in a few other close relatives of persons with typical cleidocranial dysostosis characteristic cranial symptoms have been reported as associated with normal clavicles. Since the clavicles may sometimes be normal, Fitchet's<sup>9</sup> name "cleidal dysostosis" is inadequate to cover all instances properly belonging to the syndrome.

Other defects of the shoulder girdle have been recorded. The scapula is frequently small, and the superior fossa and the coracoid process may be absent or reduced. Anomalies of the musculature have been variously described in numerous cases, but these are apparently secondary to the lack of clavicles. There are occasional anomalies of the humeral head, and 7 instances of congenital dislocation of the humerus have been reported.

The most prominent symptom is the unusual motility of the shoulders, which in some cases can be voluntarily approximated in front. At least 1 man with such a condition made his living in the circus as a contortionist, another was a ballet dancer. There is usually no functional loss in the arms. Many such persons do heavy work, and 1 youth has been photographed standing on his hands. In 6 cases weakness in the arms is mentioned, in 9 cases there was pain in the arm or shoulder, and in 4 cases paresthesias occurred in the arm.

The pelvic girdle frequently is affected. The most common pelvic anomaly, a wide symphysis pubis, is mentioned in 33 of the cases reported since 1933. The pelvic inlet may be unduly narrow and distorted (24 cases). Eleven cases in which cesarean section was necessary have been reported.

Anomalies of the legs, to which some of the reduction in stature may be ascribed, are extremely common. The literature includes at least 47 cases of genu valgum, 27 cases of coxa vara, 13 cases of pes valgoplanus and a few cases each of many other types of deformity of the lower extremities. Several patients are said to have complained of "weak legs," and several were slow in learning to walk. However, of those slow in learning to walk, at least 3 were also said to be slow in learning to talk.

Still<sup>17</sup> noticed shortening of the thumbs, and Jansen,<sup>18</sup> who noted shortening of the intermediate and terminal phalanges of the toes, widening of the latter and shortness of the nails, proposed the name "dysostosis cleido-cranio-(digitalis)" Short, tapering terminal phalanges have been reported in 66 cases of cleidocranial dysostosis Carpal, tarsal, metacarpal and metatarsal bones are also sometimes abnormal In several cases there were extra epiphyses at the base of the second metacarpal bones

There are in various cases all manner of congenital bony anomalies, but any of them may be lacking Most notable, except for the clavicular dysostosis, are the many midline defects, which range from persistence of the frontal suture to total absence of the anterior thoracic wall, with extrusion of the heart and lung, as in Morand's<sup>19</sup> case Other midline defects include persistent fontanelles, saddle nose, high, narrow palate, failure of mandibular union at the symphysis, os hyoideum bipartum, sternal defects, spina bifida occulta or spina bifida aperta, and *Spaltbecken*

#### REPORT OF A CASE

*History*—E McG, a 31 year old, single engineer, was brought to Duke Hospital by his mother because of inability to sleep and "nervousness," of about two months' duration For the past week he had been "talking out of his head" and had behaved queerly

The patient's background was that of a well regarded family of moderate means in a small town His father, aged 72, was described by the patient's mother as alert and "very much alive" despite his pronounced skeletal and dental defects His case will be described later Mrs McG mentioned that 1 of her husband's sisters and 1 of his brothers were afflicted with "mental trouble" No history of physical defects was obtainable except that the patient's paternal grandfather and the latter's sister were described as stooped in their old age There were 2 brothers of the patient, both of whom were normal physically and mentally Both were married and apparently well adjusted The mother herself seemed to be a serious-minded, hard-working person, who was interested in her children and had always been fairly ambitious for them She described herself and her husband as always having been only moderately strict with the boys Both she and her sister were physically normal

The patient's personal development was interesting in that it was much like that of his brothers except that his enuresis lasted longer, until the age of 4 years He was at times quite sensitive about his defects but played just like his brothers and stayed no more to himself than they He studied more diligently than the others, and his mother thinks that possibly he was a little slower Until he

17 Still A Case of Cleidocranial Dysostosis, Tr M Soc London **31** 350-352, 1908

18 Jansen, M Feebleness of Growth and Congenital Dwarfism, with Special Reference to Dysostosis Cleido-Cranialis, London, Oxford University Press, 1921

19 Morand Observations anatomiques, Hist Acad roy d sc **4** 476, 1776, cited by Fitchet<sup>9</sup>

became interested in radio and made a broadcasting station of his own, in which he became absorbed, she thought that he was hard of hearing. He was described as very religious, and his mother hesitated before pronouncing him as not fanatical. There had been no bad habits, such as drinking, smoking or drug addiction.

After graduating from a college of engineering, he was unable to find work as an engineer and seemed to be disturbed and nervous about it. At that time he first came to Duke Hospital to see what could be done for his dental and other difficulties. The diagnosis of cleidocranial dysostosis was made, and he was told that nothing could be done for him. His nervousness seems to have presented no features similar to the disorder responsible for his latest hospitalization. For several years he helped his father, did other odd jobs and for a little while taught school. He remained ambitious to "achieve something big" as an engineer and decided to go to New York. He learned that he had to have a hernia repaired before he could find employment. After the herniorrhaphy he worked for the electrical department of a large railroad then secured a job with Westinghouse Electrical Corporation in electrical engineering and worked toward his master's degree at Columbia University. He devoted much time to church work and Y M C A activity. He seemed to like New York, and the only disturbing incident of which his mother knew was the possibility of developments with a girl with whom he had become friendly.

For two months before admission to the hospital the patient had been nervous and had experienced difficulty in sleeping. He stayed away from work for a short time but was advised to return. He became certain that something was wrong with his heart. An electrocardiogram was normal, however. Having been granted a leave of absence, he returned home, and his condition was not "really bad" until a week before his admission to the hospital. He talked about not having known the facts of life, became very nervous, was tense but was fairly quiet. He was never destructive and did not threaten any one. He talked about the cause of his illness and wished some one had helped him. On the day before admission he urinated without going to the toilet and experienced enuresis that night.

On admission he appeared to be antagonistic and apprehensive. He sat wrapped in a heavy robe, perspiring profusely, and his teeth clacked rapidly. There were numerous stereotyped movements, and his speech was barely coherent. He stated that he could not concentrate, that he felt at times like taking his own life and that he was no good, as his genitalia were made of water and his heart was enlarged. He believed that he had just killed his parents, and he was actively hallucinated. He frankly stated that he was afraid of the hospital physicians because he thought that they had already tried to hit him on the head, and he pleaded with them not to do it again. He remarked that he was "just weak" and that he masturbated and could not stop. Since he believed that no one would help him, he would not say whether he thought he could improve, though his attitude implied that he believed his case was hopeless.

*Examination*—The patient weighed 61.5 Kg. and was 164 cm. (64½ inches) in height. His head was large and wide, with a sagittal furrow beginning at the root of the nose and extending the length of the crown. The eyes appeared large, and the sclera could be seen on all sides of the iris when the patient looked straight ahead. The nose was short and broad, and the root was flat and marked by a vertical groove, several millimeters wide, in the region of the nasion. The bridge was deficient. The middle part of the face was poorly developed, partly because of the lack of a full complement of teeth, and the mandible was prominent.

The teeth were anomalous. Seven maxillary teeth were fully erupted and two others partially so. Ten mandibular teeth were present. The probable formula was  $\frac{7\ 6\ 4\ 2}{7\ 6\ 3\ 2\ 1} \mid \frac{1\ 2\ 5\ 6\ 7}{1\ 3\ 4\ 6\ 7}$ . Because all teeth were extremely irregularly placed, the occlusion was unsatisfactory. The lower left anterior teeth had gaps between them and were rotated. The enamel on the mandibular incisors was defective. The palate was an extremely high, narrowed gothic arch, and the tooth-bearing part was much widened medially. There was a history of pavorrhea in 1935.

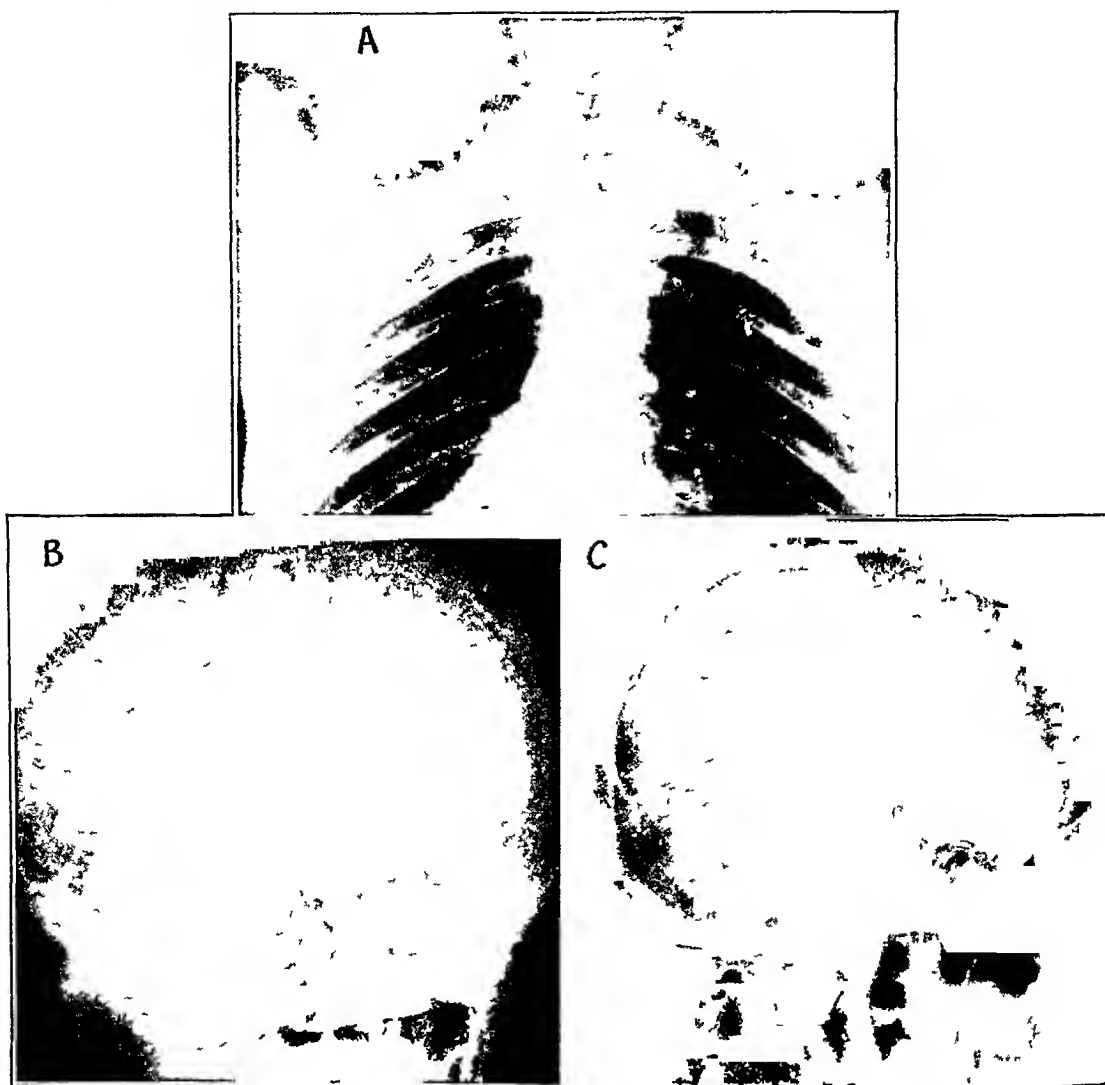


Fig 1—(the patient, E McG) *A*, roentgenogram of the chest, showing the sternal rudiment of the clavicle and spina bifida, *B*, roentgenogram of the skull (brow down), showing the frontal suture, the reduced frontal sinus, the sutural furrow and defective nasal bones, *C*, lateral roentgenogram of the skull, showing defects of the inner table, impacted third molar and other features

Roentgenograms of the patient had been taken in the outpatient department in 1935, and the generalized findings of cleidocranial dysostosis with widening of the suture lines were reported. Additional roentgenograms were taken in 1944

(fig 1), when the curvature of the dorsal region due to the narrowing of the middorsal vertebrae was noted. The general appearance was said to be that of osteochondritis of long standing.

Dr Max Eichwald, of Watts Hospital, Durham, N C, subsequently examined the roentgenograms and commented as follows: "The films are not clear. They consist of a lateral and an anteroposterior (brow down) view of the skull, views of both shoulders and of the chest and a lateral view of the vertebral column. They show a cranial cavity which is large in relation to the face, and a scaphoid,

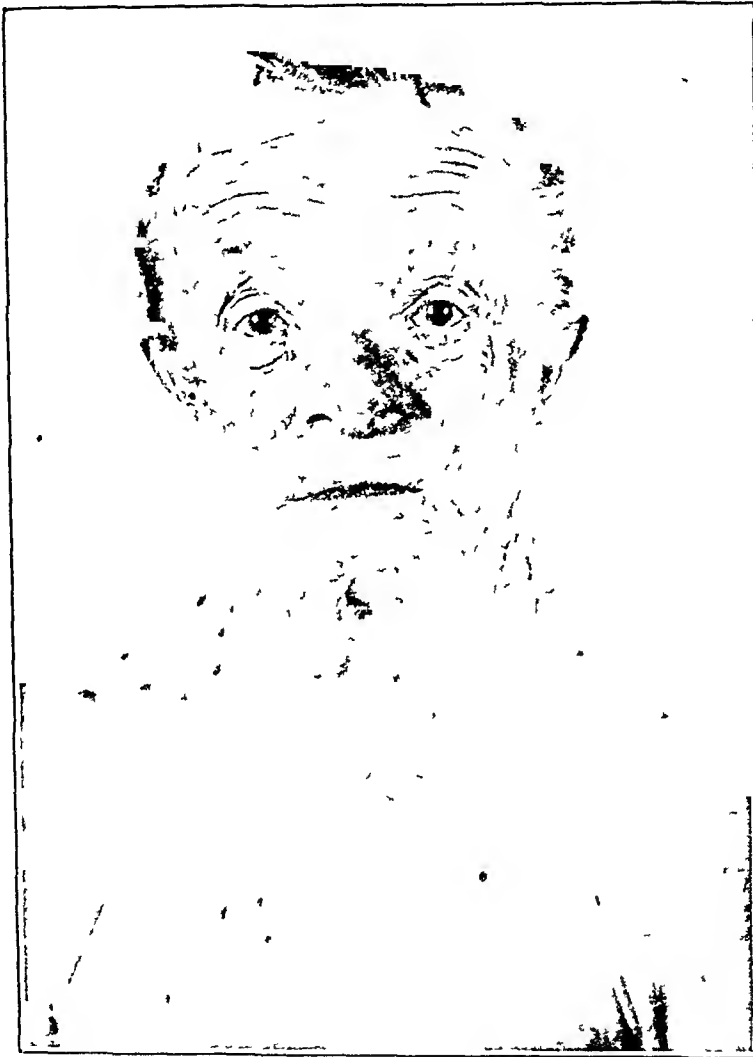


Fig 2—Cleidocranial dysostosis in the father (W McG), showing absence of clavicles, wide head and frontal furrow.

asymmetric skull with several wormian bones and a wide sagittal suture, not quite closed. Both the inner and the outer table of the skull are present except for interruption of the inner table in the posterior part of the frontal and the posterior part of the parietal region. There are flattening and anteroposterior elongation of the sella turcica. The frontal sinuses are undeveloped. On the left there is a very small nasal bone, none is present on the right. The orbits are high. One mandibular third molar is visible, unerupted and malposed. The left clavicle is represented by a short, underdeveloped sternal rudiment, which does not extend to the acromial process, and the right clavicle seems to be similar but



smaller. The scapulas are only slightly smaller than normal. The upper dorsal vertebral bodies are wedge shaped, producing marked kyphosis. Spina bifida occulta occurs in at least the lowest three cervical vertebrae (no roentgenograms were taken of the upper cervical region). The ribs are narrow. There are no cervical ribs in this case."

Neurologic examination revealed nothing significant so far as could be ascertained with poor subjective testing. The electroencephalogram, the serologic reactions and other accessory clinical findings were essentially normal.

*Patient's Father*—W McG, the patient's father, was physically similar to his son. He is pictured in figure 2, and in figure 3 he is shown with the 2 normal



Fig 3—Cleidocranial dysostosis in the father and his normal sons. The third (affected) son, E McG, is not shown.

brothers of the patient. He was 132 cm (52 inches) tall. Physical examination revealed the absence of clavicles and widening of the neck. The furrow of the forehead and crown and the wide cranial vault were typical of cleidocranial dysostosis. The fingers, especially the fifth, showed deficient growth of the terminal phalanges. An inguinal hernia was present. The teeth were all extracted about thirty years before. W McG said that he kept cutting teeth until he was 44 years old, and one upper right molar appeared still to be erupting at the time of his examination. He said he had had seventeen impacted teeth. The palate appeared normal in shape for an edentulous person. He was hard of hearing.

A summary of the readings of the roentgenograms of W McG is as follows. The thorax was narrow at its superior aspect, and the clavicles were completely absent. The roentgenogram of the skull showed that the anteroposterior and transverse diameters were increased, with the vertex flat and with wide separation of the frontal bones. In the occipital area there was inward protrusion in the region of the foramen magnum, simulating actual platybasia. The changes in the chest and skull were those of cleidocranial dysostosis.

*Course of Patient's Illness*—After a few days at the hospital, the patient, E McG, became mute and would respond only to whispered communications. At this time he had three interviews when under sodium amytal hypnosis, each of which produced successively poorer results. During the first session he talked much more freely than at any other time during his stay in the hospital. He spoke about the FBI and charges against him. He talked about his girl and indicated sensitivity concerning his physical defects in interpersonal relationships, particularly with this girl. He also talked at length, though vaguely, of participating under force in homosexual activities. He believed that he had killed his parents and remarked that he had seen the holes in his mother's legs. It was interesting that his active hallucinations disappeared during the administration of amytal and that when the effects of the drug began to wear off the hallucinations returned.

As was expected, no improvement resulted from the interviews during amytal hypnosis. For an hour or more every evening of the subsequent two or three weeks efforts were made to obtain contact with the patient. Much of the time was spent in waiting. Occasionally there appeared to be sparks of interest in some subject, but nothing came even close to taking hold of his attention. All the psychogenic material available was gradually used, with no noticeable results, and it was decided to proceed with electric shock treatment with use of curare because of his vertebral condition, a series of seventeen electric shocks was given. The first four treatments brought a great deal of improvement, but he rapidly relapsed. Then followed four more treatments at closer intervals, the response to which was only moderately favorable. After another short period, another nine treatments were given, but never did he reach the state of clarity that he had attained after the first four treatments. He was somewhat confused, and it was decided to give him a trial at home.

Nineteen months later the patient was seen briefly at his home. He said that he had been hospitalized elsewhere in the meantime and that he had received more electric shock treatments.

The patient's mother has died recently, and at the time of this report he lives alone with his father. He has not been working but seems to be able to maintain normal social relations with the neighbors. However, he admitted having auditory and visual hallucinations and said that he slept only about three hours a night. He claimed that he could be influenced from afar, that he had been killed and that he will be killed. He does not trust any one, not even his father or brothers.

A review of the literature suggests that from the psychiatric standpoint persons with cleidocranial dysostosis might almost represent a cross section of the general population. Certainly, the vast majority have normal mentality, and in at least 56 cases there has been a direct statement to this effect, such as that the patient was "intelligent." There are, of course, occasional cases in which are manifest a variety

of psychiatric disorders, such as mental deficiency, convulsive disorders, emotional instability and psychoses, and sometimes combinations of these

Unfortunately, the suggestion of a neurologic component is obscured by the meager number of reports of postmortem studies. Van Neck<sup>20</sup> reported a case in which the dura was adherent to the cranium. In Scheuthauer's<sup>21</sup> case there is said to have been cavities in the frontal lobes the size of pigeon eggs. In 1 of Marie and Santon's<sup>4</sup> cases, a man aged 39 had right hemiplegia, and his trouble was diagnosed as syringomyelia. This man died at the age of 52, and Roussy and Ameuille<sup>22</sup> confirmed the diagnosis of syringomyelia, they found a large central cavity. In the case of Voisin, de Lépinay and Infroit<sup>23</sup> autopsy was done by Leri and Tretiakoff<sup>24</sup>. They observed an inflammatory process in the brain and the meninges and a posthemorrhagic cyst. The most interesting postmortem observation from our point of view is that of Stewart,<sup>25</sup> who examined a demented woman aged 47. The frontal poles were small and extremely narrow from side to side. There was poor development of the superior frontal convolutions and of the anterior part of the corpus callosum. There was atrophy or agenesis of the cingular gyrus bilaterally, and section at this level showed absence of mature nerve cells, only a few neuroblasts, almost devoid of processes, being present. The Betz cells of the motor cortex showed chronic degeneration.

Mental deficiency occurs in a few cases of cleidocranial dysostosis. McCurdy and Baer<sup>26</sup> reported a case of such deficiency in a Negro aged 52. Still<sup>17</sup> and Heinecke<sup>27</sup> have reported cases in which the patients were slow to learn to walk and talk. Kahler<sup>28</sup> reported 2

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20 van Neck, M. Autopsie d'un cas de dysostose cleido-crânienne, *Rev d'orthop* **21** 323-332, 1934

21 Scheuthauer, G. Combination rudimentärer Schlüsselbeine mit Anomalien des Schädels beim erwachsenen Menschen, *Allg Wien med Ztg* **16** 293-295, 1871

22 Roussy, G., and Ameuille. Presentation de pieces provenant de l'autopsie d'un cas de dysostose cleido-crânienne hereditaire, *Rev neurol* **17** 815-816, 1909

23 Voisin, R., de Lepinay, M., and Infroit. Étude clinique et radiographique d'un cas de dysostose cleido-crânienne, *Nouv iconog de la Salpêtrière* **20** 227-237, 1907

24 Leri, A., and Tretiakoff. Autopsie d'une dysostose cleido-crânienne, grosses lésions inflammatoires et hémorragiques meningo-encéphaliques, *Bull et mem Soc med d hop de Paris* **47** 1091-1099, 1923

25 Stewart, R. M. The Nervous System in Cleidocranial Dysostosis. Report of a Case; *J Neurol & Psychopath* **9** 217-221, 1929

26 McCurdy, I. J., and Baer, R. W. Hereditary Cleidocranial Dysostosis, *J A M A* **81** 9-11 (July 7) 1923

27 Heinecke, P. Ueber kongenitale Schlüsselbeindefekte, *Ztschr f orthop Chir* **21** 553-571, 1908

28 Kahler, O. H. Beitrag zur Erbpathologie der Dysostosis cleidocranialis, *Ztschr f menschl Vererb- u Konstitutionslehre* **23** 216-234, 1939

cases of the condition in imbeciles and 7 in feebleminded persons Spota and Gonzales<sup>29</sup> reported an Argentinian Spaniard with dysostosis and an encephalitic reaction with stupor of narcoleptic type. Lopez Rodriguez<sup>30</sup> reported the case of a man aged 27 with cleidocranial dysostosis who was described as oligophrenic. This man had a mental age between 10 and 12 years. It is said that he had great repugnance for every effort, physical or intellectual.

Convulsive disorders are also infrequent. It is probable that some of them may be caused by the increased vulnerability of the brain to injury because of the defective brain case. Molteni<sup>31</sup> reported the case of a child of 11 years with mental deficiency and epileptiform convulsions. Crouzon and Bouttier<sup>32</sup> reported the case of a youth aged 18 who had had frequent convulsions after the age of 16. This was a classic case of epilepsy, with tongue biting, incontinence and loss of consciousness. Massee<sup>33</sup> described the case of a girl aged 15 with dysostosis and an intelligence quotient of 56.

For more than a year she has been subject to epileptic fits which she says are preceded by feeling as though the top of her head were coming off. The attacks occur in varying frequency, sometimes once or twice a day, sometimes once a week.

Stahl<sup>34</sup> reported the case of a 4½ year old girl who was an imbecile or a high grade idiot and who was partly deaf and had convulsions. In 1 of the cases of Klinke and Pahlke,<sup>35</sup> that of a female infant, tetany was said to have been cured by an antirachitic regimen. A baby reported on by Muldavin<sup>36</sup> had convulsions eight days after delivery, but these disappeared in two weeks. In 1 of Marie and Santon's<sup>1</sup> cases a brother with dysostosis died in convulsions at the age of 2½ years. Steel and Whitaker<sup>36</sup> reported the case of a 24 year old woman who

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29 Spota, B. B., and Gonzales, E. Dysostosis cleidocraneana hereditaria y familiar, enfermedad de P. Marie-Santon, *Rev. Asoc. méd. argent.* **57**:930-933, 1943.

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34 Klinke, K., and Pahlke, H. Dysostosis cleidocranialis. Bericht über zwei Fälle, *Arch. f. Kinderh.* **91**:46-54, 1930.

35 Muldavin, L. F. Craniocleidodysostosis in a Boy of Seven, *Brit. M. J.* **2**:13, 1937.

36 Steel, J. P., and Whitaker, P. H. Case of Cleidocranial Dysostosis, *Brit. J. Radiol.* **10**:613-618, 1937.

had had rare epileptic fits since the age of 17 Russo-Frattasi<sup>14</sup> reported the case of a dysostotic woman who had epileptiform convulsions after scarlet fever A 15 year old girl with cleidocranial dysostosis reported on by Dowse<sup>37</sup> had had epileptic fits from the age of 9 years She had had uncontrolled gyratory movements of one arm and had lost control of her lower limbs for a short time at the age of 12 Lechelle, Thevenard and Mignot<sup>38</sup> described the case of a man aged 29 who fell to his knees three times in one day without loss of consciousness He had a history of enuresis until the age of 6 and had a para-anal area of anesthesia Other cases in which enuresis had been reported include those of a 4¾ year old child and a 6½ year old child

In several reported cases of cleidocranial dysostosis the patients had histories of emotional disturbances Lyons and Sawyer<sup>39</sup> recently recorded a case of a person with psychopathic personality and pathologic emotionality Abram<sup>40</sup> mentioned that in his case the patient was intelligent but emotional Barber and Buchanan's<sup>41</sup> patient and 1 in the family reported on by Villaret and Francoz<sup>42</sup> were nervous Thoma and Kalil<sup>43</sup> mentioned the "acute sensitivity" of a young woman with dysostosis whom they saw Boland<sup>44</sup> reported the case of a youth who made good progress with his studies but had a "roaming disposition" In Hamilton's<sup>45</sup> case there was difficulty in sleeping Marchante and Ruiz Cestero<sup>46</sup> reported the case of a 14 year old boy whose sleep was fitful The mother of this patient volunteered the comment that the schoolmates made fun of her son and called him "Shorty"

37 Dowse, T S Congenital Deformity of Clavicles, Tr Path Soc London **26** 166-168, 1875

38 Lechelle, P, Thevenard, A, and Mignot, H Dysostose cleido-crânienne avec malformations vertebrales multiples et troubles nerveux caractere familial des malformations, Bull et mem Soc med d hôp de Paris **52** 1526-1530, 1936

39 Lyons, C G, and Sawyer, J G Cleidocranial Dysostosis, Am J Roentgenol **51** 215-219, 1944

40 Abram, J H Cleido-Cranial Dysostosis, Lancet **2** 429-431, 1907

41 Barber, W W, and Buchanan, L D Congenital Absence of Both Clavicles and Malformation of Cranium (Cleidocranial Dysostosis), Colorado Med **29** 196-201, 1932

42 Villaret, M, and Francoz, L Une famille de quatre sujets atteints de dysostose cleido-crânienne hereditaire, Nouv iconog de la Salpêtrière **18** 302-343, 1905

43 Thoma, K H, and Kalil, F H Clinic of Dental Department of Massachusetts General Hospital and Department of Oral Surgery, Harvard School of Dental Medicine, Am J Orthodontics (Oral Surg Sect) **29** 513-588, 1943.

44 Boland, M A Case of Rudimentary Clavicles, J A M A **58** 1442 (May 11) 1912

45 Hamilton, W F A Case of Congenital Deficiency of Both Clavicles, Philadelphia M J **4** 720-721, 1899

46 Marchante, R F, and Ruiz Cestero, G Congenital Cleido-Cranial Dysostosis Report of Case, Bol Asoc med de Puerto Rico **36** 103-108, 1944

Besides our case, only 3 cases of the condition associated with a psychosis have been described. Krabbe<sup>47</sup> described a man aged 28 who gave the impression of having a psychomantile personality. He had slightly persecutory ideas and was somewhat deluded. His orientation and mood were satisfactory. Eldridge, Simon and Ramos<sup>7</sup> redescribed the case of a 55 year old white man which had been previously reported by Cavanagh<sup>48</sup>. He had suffered from dull headaches and partial deafness for twenty-two years. He had auditory hallucinations, memory defects, impaired judgment, disorientation and unsystematized paranoid delusions. This man talked little, but coherently, and was quiet and seclusive. His Stanford-Binet score was at the 8 year 11 month level, with considerable scatter.

The case in which the postmortem observations were described by Stewart<sup>25</sup> had been reported previously by Lavery<sup>49</sup>. He stated

The patient's mental condition is one of partial dementia. She recognizes her surroundings, but has no idea of time. She gives her age as 17. Objects such as a book, coin, pencil, are correctly named, and she is able to write her name. She has illusions of mistaken identity and she states that her mother is in the ward. She makes no attempt to occupy herself, and at times screams loudly for no apparent reason. She feeds, dresses and washes herself, and is in the habit of hoarding rubbish. Probably at one time she had a fair amount of intelligence, but is gradually deteriorating.

This patient had motor weakness and slight spasticity of the lower limbs. She could not stand without assistance, and the strength of the knee jerk was diminished.

In view not only of the rarity and diversity of psychiatric disturbances but also of the dissociation of cleidocranial dysostosis and psychiatric disorders in families, the relationship of the two conditions does not seem an intimate one. In the family we have studied 1 of the dysostotic members has schizophrenia but the other is psychiatrically normal. Similarly, Frets<sup>50</sup> recorded 2 families in which cleidocranial dysostosis, on the one hand, and convulsions, nervousness, imbecility and insanity, on the other, occurred independently in various members. Rhinehart's<sup>13</sup> patient, though slow in school, was mentally alert, but a sister without bony anomalies was an idiot and had spastic paralysis. Kahler<sup>28</sup> reported that, in addition to 9 cases of mental deficiency among 15 persons with cleidocranial dysostosis, there were also 4 cases

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47 Krabbe, K. H. Dysostosis Cleidocranialis with Metabolic Disturbances, *J. Nerv. & Ment. Dis.* **61** 18-30, 1925.

48 Cavanagh, J. R. Cleidocranial Dysostosis. Report of Case, *M. Ann. District of Columbia* **3** 11-13, 1934.

49 Lavery, S. J. Cleidocranial Dysostosis (Anosteoplasia), in *Annual Report of the Metropolitan Asylum Board, London, 1924-1925*, vol. 27, pp. 261-262.

50 Frets, G. P. Two Cases of Hereditary Dysostosis Cleidocranialis, *Genetica* **12** 513-530, 1930.

of feeble-mindedness and 1 of imbecility among 16 brothers and sisters without dysostosis. He explained this by stating that the earlier generations of dysostotic members were mentally fairly normal but that they had succeeded in finding spouses only among the mentally deficient.

#### SUMMARY

Cleidocranial dysostosis is a rare developmental disease of the skull, bones of the face, teeth, clavicles, vertebrae, pelvis and phalanges, in fact, it sometimes involves the whole skeleton. The condition ordinarily is inherited as a mendelian dominant. Its incidence is similar in the two sexes and in all races and age groups.

In few of the reported cases were the patients suffering from mental disease. The psychosis in the case here reported manifests connection with the dysostosis only in certain portions of the content and differs in no essential way from the recognized form of schizophrenia. It is evident that the patient's psychologic reactions to his peculiar physical appearance provided the basis for much of the color of the content.

This is in agreement with the impression one gets from a reading of the previously reported cases. In the few persons with mental disease no constant relationship to the dysostosis has been established. The incidence of minor psychiatric disorders in persons with cleidocranial dysostosis is even less frequent than one might have expected considering the social implications of such prominent physical abnormalities.

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## ELECTRICAL PARESTHESIAS IN THE EXTREMITIES FOLLOWING INJURY TO THE CENTRAL NERVOUS SYSTEM

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THE condition known as "the electrical sign," or "Lhermitte's symptom," is a rare manifestation of disease of the central nervous system. Patients with the full blown syndrome complain that on bending the head and neck forward paresthesias begin in the base of the neck and radiate into the upper extremities, down the spine and, finally, into the lower extremities. The sensation is variously described as "vibrating," "just like sticking your finger into an electric socket" or "like bumping your funny bone."

In 1918 Babinski and Dubois<sup>1</sup> described the syndrome as a sequela of injury to the neck. One year previously they had reported similar disturbances following head injury. Between 1922 and 1929 Lhermitte and associates<sup>2</sup> reported that the syndrome was also found in cases of multiple sclerosis. It was Lhermitte's original opinion that it occurred as an early symptom of this disease, but this has been disputed by others. Since Lhermitte's original work, other observers<sup>3</sup> have reported a

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1 Babinski, J, and Dubois, R. Pains in the Form of an Electrical Discharge Following Injuries to the Neck, *Presse med* **26** 64, 1918, cited by Salmon<sup>3f</sup>

2 (a) Lhermitte, J, and Cornil, L. Heteresthesia Associated with Direct Concussion of the Spinal Cord, *Encéphale* **17** 201, 1922, cited by Salmon<sup>3f</sup> (b) Lhermitte, J, Bollack, and Nicolas, M. Pains Similar to an Electrical Discharge Following Head Flexion as a Symptom of Multiple Sclerosis, *Rev neurol* **31** 56 (July) 1924, cited by Lhermitte<sup>2d</sup> (c) Lhermitte, J, Levy, G, and Nicolas, M. Electrical Discharge Sensations as an Early Symptom of Multiple Sclerosis, *Presse med* **35** 610 (May 14) 1927, cited by Lhermitte<sup>2d</sup> (d) Lhermitte, J. Multiple Sclerosis. The Sensation of an Electrical Discharge as an Early Symptom, *Arch Neurol & Psychiat* **22** 5 (July) 1929

3 (a) Bericl, L, and Devic, A. Electrical Discharge Sensations in a Case of Multiple Sclerosis, *Lyon méd* **141** 559, 1918, cited by Salmon<sup>3f</sup> (b) Trioumphoff, A. Electrical Discharge as a Symptom of Multiple Sclerosis, *Presse méd* **35** 948 (July 30) 1927, cited by Lhermitte<sup>2d</sup> (c) Roger, H, Reboul-Lachaux, J, and Aymes, G. Meningeal Dysesthesias Similar to Electrical Discharge on Flexion of the Head as a Symptom of Multiple Sclerosis, *Rev neurol* **1** 1052 (June) 1927, cited by Lhermitte<sup>2d</sup> (d) Wechsler, I S. A Case of Multiple Sclerosis with Unusual Symptoms, *Arch Neurol & Psychiat* **19** 364 (Feb) 1928, cited by Lhermitte<sup>2d</sup> (e) Opalski, A. Paroxysmal Paralysis (Sensations of Electrical Discharge) in a Case of Multiple Sclerosis, *Rev neurol* **1** 281 (March) 1931 (f) Salmon, L A. The Sensation of Electric Shock in Multiple Sclerosis, *Bull Neurol Inst New York* **6** 378 (Aug) 1937



number of cases of multiple sclerosis in which this symptom appeared. It has also occasionally been reported in cases of tumor or tuberculosis of the cervical portion of the spinal cord and of subacute combined sclerosis of the spinal cord<sup>4</sup>. However, since the earlier reports of the World War I, few cases of the syndrome occurring after trauma to the head or neck have been recorded<sup>5</sup>. It is the purpose of this paper to report a series of such cases seen in a large Army neurosurgical and neurologic center.

Triumfov<sup>6</sup> has recently reported the syndrome in 23 cases of head injury. The wound was occipital in 7 of these cases, parieto-occipital in 5, temporal in 2, temporoparietal in 2 and coronal in 2. The dura mater was involved in 20 cases. He stated the opinion that the intensity probably depends on the proximity of the wound to the foramen magnum and that the syndrome may be the result of injury to the spinal nerve roots or to formation of scar tissue and adhesions in the meninges. He found that the sensation was more severe in the extremity on the side of the injury, that the onset was gradual at the time of healing of the wound (or two or three weeks later) and that the syndrome disappeared gradually in one or two months. In his report, he pointed out that some of the patients experienced a sensation of "weakness" in the distribution of and for the duration of the paresthesia. He found some of his patients considerably disabled by the syndrome, even to the extent that it was necessary for them to hold the head in a fixed position.

#### REPORT OF CASES

CASE 1—A private aged 35, on Oct 14, 1944 sustained a penetrating wound of the right temporofrontal region with a compound, comminuted fracture of the right frontal bone and a lesion of the anterior portion of the second and third frontal convolutions. Foreign bodies were removed from the right frontal lobe. He became ambulatory about Dec 15, 1944.

At the time of admission to an Army general hospital, on Jan 22, 1945, he was complaining of occasional headaches and "dizziness" and some pain in the lower part of the back. A few days after admission he began to notice that on bending his head forward he experienced a feeling "like electricity," which began in the low thoracic and upper abdominal regions bilaterally, radiating upward, then into both upper extremities and, finally, out to the fingers. The sensation did not ascend as high as the face, did not appear in the lower extremities and disappeared as soon as he straightened his neck.

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4 Hassin, G. B. Paraplegia in Flexion and the Symptom of Lhermitte, *Arch Neurol & Psychiat* **29** 855 (April) 1933, cited by Salmon<sup>3f</sup>.

5 Brown, T. G. A Case of Concussion of Spinal Cord Resultant on a Graze by a Live Shell, with Especial Reference to the Phenomenon of "Heteresthesia," *J Neurol & Psychopath* **1** 54 (May) 1920, cited by Salmon<sup>3f</sup>.

6 Triumfov, A. V. The Symptom of "Electrical Discharge" in Brain Injuries, *Am Rev Soviet Med* **2** 350 (April) 1945.

Examination disclosed a right temporal and a frontal cranial defect, hypesthesia of the scalp in the distribution of the right supraorbital nerve, slight reduction in vibratory sensation over the entire left side of the body and reduction in abdominal reflexes on the right side. No cervical roentgenogram was taken.

The patient continued to experience the symptoms of electrical discharge until March 3, 1945, at which time the cranial defects were closed with tantalum plates. After this operation the sensations disappeared. He was discharged from the hospital on June 25, 1945. A follow-up note from the patient, dated November 21, stated that the paresthesias had not recurred.

CASE 2—A soldier aged 22 was wounded by shell fragments on Nov 24, 1944. One fragment caused a compound fracture of the right frontal bone, penetrated the brain and came to rest in the left middle fossa of the skull. Another fragment lacerated the right mastoid region. He suffered immediate left hemiparesis, but this rapidly disappeared. After the wound the patient continued to complain of recurrent generalized headaches. He became ambulatory about Jan 8, 1945.

About Feb 15, 1945 he began to note that when he bent his head forward he had a "fluttering sensation," of equal intensity on the two sides, which appeared simultaneously in the upper part of the chest and on the medial sides of the upper and lower extremities. The sensation radiated from the proximal to the distal portions of the extremities, and the patient experienced difficulty in using the extremities during the time that the sensation was present. The sensation was more pronounced after he had held his neck straight for some time. Thus, his symptoms were particularly severe after being in a picture show, when the neck had been immobile for some time. He stated that if he kept his neck bent the sensation finally disappeared, seeming to disappear everywhere at once. He described the sensation as "a kind of an inside shudder, something like an electrical feeling."

The patient was admitted to an Army general hospital on Feb 14, 1945. Examination disclosed a right frontal cranial defect and a questionable Oppenheim sign bilaterally. The electroencephalogram was normal. No roentgenogram of the cervical portion of the spine was taken.

Cranioplasty was not performed. He was discharged from the hospital August 24.

CASE 3—On Dec 2, 1944 a soldier aged 21 sustained a wound from a shrapnel fragment, causing a compound, depressed fracture of the left temporal bone. He immediately lost consciousness and except for two or three short lucid intervals was disoriented for several days. Overseas records indicated that some verbal aphasia was present at first, but this had disappeared by the time of his admission to the Army general hospital, on March 9, 1945. The depressed fracture was elevated, and debridement was performed at a forward installation. He became ambulatory in late December 1944.

About March 1, 1945 he first noted that on bending his head forward he had a "jittery, electric feeling" radiating down the back of his arms and forearms, into the index fingers bilaterally and also into the epigastrium. The sensation appeared to begin spontaneously in the epigastric region, without radiation around from the spine. At no time did he experience any similar sensations in the lower extremities. If he bent his head forward and held it there, the symptoms would disappear within a few seconds. Bending his head forward several times in succession did not appear to decrease the intensity of the symptoms.

Examination disclosed a suggestion of dyspraxia in the right hand, impaired auditory acuity and right homonymous superior quadrantanopsia. A 2 by 3 cm

defect was present in the left temporal bone. Roentgenograms of the cervical portion of the spine were normal except for slight asymmetry in the atlantoaxial joint, which was probably due to position. The electroencephalogram was abnormal, showing generalized dysrhythmia with focal damage in the left temporo-occipital region.

The patient's symptoms continued unabated throughout March and April 1945, and then they slowly decreased in intensity and frequency and disappeared about June 1, 1945. A tantalum cranioplasty was performed May 24. He was discharged from the hospital June 18, 1945.

**CASE 4**—A soldier aged 23 was struck in the right temporal region by a sniper's bullet on June 21, 1945. The bullet passed downward and made its point of exit in the left inframandibular region. Transient paralysis in the upper branches of the right facial nerve occurred. He became ambulatory about July 10.

Ever since sustaining the wound, he had noted mild, generalized headaches, which were relieved by lying down and were gradually improving. About September 1 he noted that when he bent his head forward he had a sensation of shock in his back. This sensation radiated into both upper and lower extremities.

He was admitted to an Army general hospital August 20. Examination revealed nothing abnormal except for a tender scar in the right temporal region. The patient was examined in detail with regard to the electrical paresthesias. By actual timing during the examination, the electrical sensation appeared in the upper extremities one second after bending the head forward and in the lower extremities two seconds later, and it had disappeared completely in about five seconds. The sensation became progressively less intense on bending the head several times in succession. In the upper extremities the sensation radiated into the ends of the fingers, and in the lower extremities it was particularly intense in the calves. No roentgenogram of the cervical portion of the spine was taken.

Cranioplasty was not performed. The patient was discharged from the hospital November 6. A follow-up letter from the patient, dated November 19, stated that he continued to have the electrical sensations, though they were somewhat less marked and that they became more intense after much exercise.

**CASE 5**—A private first class aged 20 was wounded by shrapnel fragments on Feb. 9, 1945, sustaining a compound, comminuted fracture of the occipitoparietal region of the skull. He lost consciousness and on regaining consciousness had paralysis of the left upper extremity and complained of scotomas and of hyperesthesia over the entire face and neck. The hyperesthesia and monoplegia disappeared completely in one week, but headaches and postural dizziness persisted until about May 7.

He became ambulatory about April 15, two days later he began to notice that when he bent his head forward he had a sensation "like something running around" in the hypogastric region on each side. Since that time the sensation had spread, and by the time of his admission to the Army general hospital it was described as "like a live wire" and occurred only on his bending the head forward. It would appear in the epigastric region, then radiate to the medial surfaces of the upper extremities and out to the ulnar fingers, simultaneously radiating downward to about the level of the inguinal ligaments bilaterally. The sensation had a duration of three or four seconds. The patient stated that the more rapidly he bent his head the more pronounced was the sensation. If he bent his head slowly, the sensation was not so intense, and after he bent his head several times the sensation would disappear, but would reappear after a period of holding

the neck straight. The symptoms were particularly severe after picture shows, owing to the prolonged immobility of the neck.

Except for a right parieto-occipital cranial defect, the physical and neurologic status was entirely normal on his admission to the Army general hospital on May 19. A roentgenogram of the cervical portion of the spine showed anterior angulation of the entire midcervical part of the spine.

A tantalum cranioplasty was performed on August 8. By August 13 the sensation of electrical shock was less pronounced but had the same distribution. By that time it had also been noted that the sensation could be reproduced by percussion of the spine from about the sixth cervical to the fourth thoracic vertebra. The patient was discharged from the hospital on Sept 10. A follow-up letter from the patient, dated November 19, stated that the electrical paresthesias had gradually diminished and had been absent since about October 19.

CASE 6—A soldier aged 38 was struck in the right occipital region by shrapnel fragments on Nov 27, 1944 and lost consciousness momentarily. On regaining consciousness he noted impaired vision. Examination at forward installations showed no evidence of skull fracture but did disclose left homonymous paracentral scotomas, which persisted.

About April 10, 1945 he began to note that on bending his neck forward he had a sensation "like electricity" radiating into his extremities. This was a distally radiating, "tingling, electric sensation, just like touching a spark plug," which appeared first in the hands and neck and next in the thighs. The sensation did not radiate down the spinal column. If he bent his head forward and held it bent, the sensation would disappear gradually, leaving the lower extremities first. From the time of bending his neck forward to the time of disappearance of the sensation from his lower extremities was about four seconds. If he bent his neck several times in succession, the sensation became progressively less intense, but after a period of holding his neck straight the sensation regained its original intensity. He had no headaches or "dizziness."

The patient was admitted to an Army general hospital March 16, 1945. Examination revealed that the deep reflexes of the left upper extremity were slightly hyperactive. Left homonymous paracentral inferior quadrantic scotomas were present. Slight volitional and emotional weakness was observed in the left lower part of the face. A roentgenogram of the cervical portion of the spine showed congenital fusion of the second and third vertebral bodies but no other abnormality. The electroencephalogram was normal.

The patient was discharged from the hospital on May 28.

CASE 7—A soldier aged 29 sustained penetrating wounds from shell fragments on Oct 16, 1944, with a resulting compound, comminuted, depressed fracture of the left occipital bone. The overseas operative note indicated that contusion of the superior longitudinal sinus with possible thrombosis was present. Initially on the left side there were changes in superficial sensation over the face and the upper extremity with mild hemiparesis. The patient had one generalized convulsive seizure on Oct 20, 1944.

About Dec 20, 1944 he began to note that on forward bending of the head an "electrical shock sensation" would appear in the back of his neck on the left side and radiate into both upper extremities and then into the trunk and the lower extremity on the left. The patient stated that the sensation was "just like sticking your finger into an electric socket" and that it came only when he bent his head forward.

He was admitted to an Army general hospital Jan 22, 1945. Examination disclosed hypesthesia and hypalgesia of the left side of the face and of the body above the fourth dorsal segment, with sparing of the seventh cervical segment. The deep reflexes in the left upper extremity were more active than those in the right. There was general contraction of the visual field with paracentral scotomas on the 270 degree meridian bilaterally, mild paresis of the left side of the face of central type and mild deafness in the left ear. No cervical roentgenogram was taken.

The patient was discharged from the hospital on May 12, 1945, after a tantalum cranioplasty, performed March 7.

CASE 8—A soldier aged 29 was struck by shrapnel fragments on Jan 2, 1945, sustaining fractures of the left humerus and of the left occipital bone. The humerus healed uneventfully, and the skull fracture was debrided at forward installations. He continued to complain of recurrent headaches and defective vision.

In February 1945, shortly after he became ambulatory, he noted that whenever he moved his head, particularly when he bent it forward, he experienced "shocklike, tingling sensations," generally beginning in the head and radiating through the entire trunk into the lower extremities. The sensation spread "like a wave," never involved the upper extremities and lasted only one or two seconds. It would occur the first time he bent his head but would not recur on successive bending until after he had held the neck straight for a time.

He was admitted to an Army general hospital Jan 30, 1945. Examination disclosed a right homonymous lower quadrantanopsia and a left occipital cranial defect. An electroencephalogram showed a moderate amount of unlocalized 15 to 20 per cent dysrhythmia. Roentgenograms showed multiple small metallic foreign bodies in the left posterior fossa beneath the cranial defect and anterior angulation at the level of the fourth and fifth cervical vertebrae.

A tantalum cranioplasty was performed on May 4, 1945. He was discharged from the hospital Nov 17, 1945.

CASE 9—On April 18, 1945 an officer aged 28 sustained a shrapnel wound, the fragment entering to the left of the midcervical portion of the spine and passing medially to emerge in the suboccipital region in the midline. He sustained a linear fracture of the left parietal region at the same time. He was unconscious for twenty-four hours and on regaining consciousness noticed weakness in the left upper extremity, stiffness and pain in the neck and numbness of the left hand. About June 2, 1945, the feeling of numbness spread to his right hand, and he began to experience a constant tingling sensation in both hands. No objective sensory findings were noted at this time. The weakness in the left upper extremity improved. On April 19 he had a generalized convulsive seizure but has had none since. He became ambulatory in May 1945.

He was admitted to an Army general hospital on June 17, 1945 and shortly thereafter began to notice that when he bent his head forward the tingling sensation in his upper extremities would become exaggerated and would also appear simultaneously in the interscapular region, the spine and the left lower extremity. He described the sensation as "a sort of glow which seems to radiate out," and he stated that it was "similar to the feeling obtained from a shocking machine."

On admission he complained of the paresthesias and of mild, recurrent occipital headaches and postural dizziness. Examination revealed diffuse weakness of the left trapezius muscle and the left arm and forearm (somewhat greater in the muscles innervated by the lower cervical segments). The deep reflexes of the upper and lower extremities on the left were more active than those on the right.

An electroencephalogram, a roentgenogram of the cervical portion of the spine, lumbar puncture and a Pantopaque (an iodized poppyseed oil) cervical myelogram all revealed a normal status.

During his stay in the hospital, the numbness in his upper extremities decreased and was finally noted only in the tips of the fingers on the right and in the entire hand on the left. The headaches disappeared, and the stiffness of the neck improved. He was discharged from the hospital Oct 20, 1945. A follow-up letter from the patient, dated Nov 21, 1945, disclosed that the electrical paresthesias had been absent since about Sept 15, 1945.

CASE 10—A soldier aged 21 on May 2, 1945 was struck by an enemy rifle bullet, which entered the left lower part of the neck and made its exit through the mouth. As a result of this, he sustained a comminuted fracture of the third cervical vertebra with subluxation of the second cervical vertebra on the third and of the third cervical vertebra on the fourth. Immediately after he sustained this wound, he remembered being able to clench his fists but was unable to move his arms or legs. One-half hour later, while being evacuated, he sustained additional shell fragment wounds in the left arm, the right cheek and the occipital region of the skull, the last not causing fracture. Pain in the shoulder, neck and occipital region on the left side began after this and persisted. About May 10 the tetraplegia began to subside and completely disappeared except for weakness of the left upper extremity in abduction.

He became ambulatory on May 18, 1945. About July 1, he began to notice a "sort of buzzing" sensation throughout his body, which occurred chiefly at night, after he was tired. When he bent his head forward, the buzzing sensation appeared in the back of the neck and radiated into the upper extremities, possibly appearing in the left arm first and being most intense in the fingers. It then appeared in the chest and abdomen but did not radiate into the lower extremities unless he was standing. The sensation spread "like a wave" and was described as similar to an electrical shock. When the patient was seated, it occurred in the upper extremities and the chest, but when he was standing, it appeared in the chest and the lower extremities.

The patient was admitted to an Army general hospital June 23, 1945. Physical examination disclosed some limitation of motion of the neck and, on the left side, weakness of flexion at the elbow, of supination of the forearm and of trapezius function. There was hypesthesia of the left hand generally. The tendon reflexes were more active in the left upper extremity than in the right, and Babinski and Chaddock signs were present bilaterally, with an Oppenheim sign on the left. Slight paresis of the left side of the tongue was present, and there was hypalgesia in the distribution of the supraclavicular nerves on the left. Roentgenograms of the cervical portion of the spine taken May 21 showed an abnormal curvature with step formation between the second, third and fourth cervical vertebrae, indicative of dislocation.

The patient was discharged from the hospital Aug 4, 1945. In a follow-up letter, dated Nov 19, 1945, the patient stated that the electrical paresthesias had shown great improvement and occurred only when he was unusually fatigued or when he bent the head forward forcibly.

CASE 11—On March 1, 1945 an officer aged 31 was struck by a shell fragment, which entered the left posterior aspect of the neck and passed to the right and anteriorly, producing an incomplete fracture of the first cervical vertebra and lodging in the tissues of the neck on the right. Immediately after the wound complete sensory and motor loss below the level of the lesion occurred, but

within one-half hour he was able to move all four extremities and sensation returned. He became ambulatory March 20. At the time of admission to an Army general hospital, on June 22, he had improved but continued to complain of pain in the neck and the right shoulder.

Since the first week of May 1945 he had experienced a constant tingling sensation in the tips of the fingers bilaterally. About May 15 he noticed that when he bent his head forward he experienced a sensation like an electrical shock, which began in both elbows and radiated downward into the tips of the fingers. Occasionally, when standing erect, he had the same sensation in the hypogastric region, with occasional radiation into the anterior surfaces of the thighs. The sensation never occurred unless he bent his head forward and then began almost immediately and persisted for about three seconds. There was no tendency for the sensation to "wear out" on successive bendings of the head. The sensation was more intense in the evening than in the morning and tended to become more pronounced after considerable physical exertion.

Examination revealed atrophy of the right posterior cervical muscles and some of the muscles of the right shoulder girdle. These same muscles were paretic. The tendon reflexes in the right extremities were more active than those in the left, and the right upper abdominal reflex was reduced. Roentgenograms of the cervical portion of the spine, taken May 23, showed an old fracture of the right side of the lamina of the first cervical vertebra.

He was discharged from the hospital July 19. A follow-up letter from the patient, dated Nov. 27, stated that the electrical paresthesias disappeared from the lower extremities in August and at the time of the letter were hardly noticeable in the upper extremities.

CASE 12—On May 7, 1945 a soldier aged 24 was struck in the left infraclavicular region by a bullet, which made its exit in the left suprascapular region. As the result of this wound, there developed left hemothorax and complete paralysis of the left upper extremity, due to an injury of the left brachial plexus. He became ambulatory about May 22. About August 1 he began to note that when he bent his head forward he had electrical sensations radiating down the spine and into the lower extremities. He never experienced this sensation in his upper extremities. He observed that it occurred every time he bent his head forward and did not "wear out" on bending the head several times in succession. It occurred while he was sitting, lying or standing and persisted as long as his head was bent forward.

On admission to the Army general hospital, on June 18, there was complete paralysis of all muscles of the left upper extremity with the exception of those supplied by the eighth cervical and the first thoracic root. On the left side, anesthesia was present over the distribution of the second and third cervical nerves, on the lateral aspect of the shoulder girdle and over the lateral aspect of the arm and forearm. Roentgenograms showed slight anterior angulation at the level of the second and third cervical vertebrae and healing fractures of the posterior portion of the first and second left ribs.

Exploration of the brachial plexus on September 4 showed extensive involvement of the brachial plexus with scar tissue, particularly of the fifth and sixth cervical roots. On the same date a plastic revision of the scar on the left side of the neck was done, and his neck was immobilized for some time. After this operation the electrical paresthesias disappeared. On November 14 the electrical paresthesias were still absent, and he had noted considerable improvement in motor function in the left upper extremity.

CASE 13—A soldier aged 21, on Nov 18, 1944 was wounded in the neck by a machine gun bullet, sustaining a compound, comminuted fracture of the fifth, sixth and seventh cervical vertebrae. Immediate paralysis of all four extremities occurred, but all motor function returned in fifteen minutes except in the left upper extremity, where paresis and paresthesia persisted. On November 20 a laminectomy was done. It was found that there was some compression of the spinal cord by the depressed lamina of the seventh cervical vertebrae, and the fractures had obliterated the intervertebral foramen between the sixth and the seventh cervical vertebra on the left. Sensation in his left upper extremity improved for a time after the laminectomy, but about Dec 20, 1944 he began to notice beginning loss of superficial sensation in the right hand. At the same time he noted that on bending his head forward he had paresthesias "like electricity" radiating down the dorsal surface of his arms and forearms and down the posterior surface of the thighs. There was no radiation into the chest or abdomen. He also observed that on bending his neck forward he had a "pulling" sensation in the ulnar fingers of the left hand.

Examination on March 14, 1945 disclosed generalized weakness of the right upper extremity with paralysis of the extensor carpi ulnaris and probably the opponens pollicis muscle. The radial reflex was more active on the right, and Hoffmann's sign was present on the right side only. Hypesthesia and hypalgesia were noted in the third, fourth and fifth fingers of the right hand, with paresthesia of the volar surface of the thumb and the index finger of the same hand. In the left hand there were paresthesia of the index finger and some paresthesia of the thumb. Otherwise, the neurologic condition was normal. Roentgenograms of the cervical portion of the spine showed a comminuted fracture of the fifth cervical vertebra, multiple small metallic foreign bodies and evidence of a laminectomy.

After admission to an Army general hospital, on Feb 27, 1945, the patient's electrical paresthesias gradually diminished in frequency and intensity and disappeared completely about April 15, 1945, approximately four months after the onset. He continued to complain of pain and dysesthesia in the index finger of both hands. He was discharged from the hospital July 20, 1945.

CASE 14—On Nov 14, 1944 an officer aged 37 was struck in the right supraclavicular space by a motor shell fragment, which passed down along the ribs and spine, fracturing the fourth and fifth ribs and emerged at this level directly over the spinous process of the fifth thoracic vertebra. An immediate paralysis of all four extremities ensued, with complete loss of sensation below the level of the clavicle. These symptoms disappeared completely in one-half hour. About December 14 he became ambulatory.

On Feb 2, 1945 he first noted sudden onset of a tingling sensation, "like an electric shock," beginning simultaneously in the inguinal region bilaterally and on the medial surface of the thighs and legs. This occurred whenever he exerted pressure against the scar of exit or whenever he anteflexed his shoulders. The sensation did not "wear out" with repeated production. After a long truck ride he would experience a continuous tingling sensation like electricity in the described areas, which would last about fifteen minutes. Slight weakness in the lower extremities was associated with this tingling sensation.

The patient was admitted to the Army general hospital June 14, 1945. On examination he was normal except for the scar. Roentgenograms of the cervical portion of the spine were not taken but those of the thoracic region showed fracture of the costal processes of the fourth, fifth and sixth thoracic vertebrae on the right.



The electrical paresthesias gradually became less intense and by June 1945 were not present unless the patient became unusually fatigued. He was discharged from the hospital on August 20. A follow-up letter from the patient, dated November 26, stated that the paresthesias were about the same and were present only in his lower extremities. He stated that he did not notice them unless he was very tired or unless he had taken a long, rough ride in some sort of vehicle. Cold weather seemed to aggravate the complaints.

#### COMMENT

In the cases here reported, the primary wound involved only the head in 8 patients, the head and neck in 2 patients and only the neck in 4 patients.

In patients sustaining some injury to the head, the site of the wound was as follows: frontotemporal, 2, temporal, 2, parietal, 1, occipito-parietal, 1, occipital, 4. This distribution tends to confirm Triumfov's<sup>6</sup> observation that the syndrome was more frequently associated with posterior than with anterior head wounds.

In the patients who sustained injury to the neck, the site of the lesion was equally distributed in the upper, middle and lower cervical regions.

Of the 10 patients suffering wounds of the head, definite evidence of injury to the brain was present in 8. Of the patients wounded in the neck, evidence of damage to the spinal cord was present in all but 1, and this patient had an injury to the brachial plexus. Four of the patients with wounds of the neck had transient initial tetraplegia.

Analysis of the distribution of the paresthesias indicates that in cases of anterior head wounds the paresthesias are more likely to be limited to the upper extremities and trunk, in cases of posterior head wounds, to the trunk and lower extremities, and in cases of wounds of the neck, to the upper extremities, trunk and lower extremities. It was also noted that in cases of cervical injuries the paresthesias might appear in the neck, upper extremities and trunk while the patient was seated and in the trunk and lower extremities while he was standing. In some instances the sensations did not appear in the trunk at all, while in others they appeared to radiate down the spine.

The average onset of the paresthesias was seventy-five days after the injury, but they appeared as early as thirty-two days and as late as one hundred and thirty-three days. In this series they never appeared until two to sixty-eight days after the patient had become ambulatory (average, forty-one days). After the onset, the duration of the symptoms was variable, sometimes disappearing in a month and sometimes persisting for six months. The disappearance was gradual except in 2 cases, in which symptoms disappeared suddenly after incidental operative procedures.

The electrical paresthesias appear to be the result of injury to the cervical portion of the spinal cord or its membranes, even when the

obvious injury is to the head. This contention is supported by the fact that, in the present series, in 2 of the 10 cases of head wounds there was clinical evidence of concomitant injury to the spinal cord and that, of 6 cases in which roentgenograms of the cervical portion of the spine were taken, evidence of abnormality appeared in 4. The exact pathogenesis of the symptoms is uncertain. Tinel, cited by Salmon,<sup>17</sup> expressed the belief that demyelinated sensory neurons might give rise to such symptoms when they were slightly distorted, as in bending the head or neck. This explanation appears to be as satisfactory as any that can be offered at present.

#### SUMMARY

Pertinent literature on "Lhermitte's symptom" or the "electric sign" is reviewed.

The syndrome is characterized by electrical-like paresthesias radiating into the trunk and extremities on bending the head forward. It is most common with multiple sclerosis and trauma to the head and cervical region of the spine but does occur with other diseases of the spinal cord.

The exact pathologic basis of the condition is unknown, but it appears likely that it results from alterations in the sensory tracts of the cervical portion of the spinal cord. In the cases of trauma to the head and neck reported the paresthesias appeared from a few days to two months after the patient became ambulatory and persisted for one to six months, disappearing gradually.

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# HISTOLOGIC STUDY OF THE BRAIN IN EXPERIMENTALLY INDUCED ACIDOSIS

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IN PREVIOUS experiments<sup>1</sup> it was demonstrated that lowering the  $p_H$  of the blood led to impairment of excitability of the nervous system to electrical stimulation. The greatest reductions in excitability occurred in reflex arcs. Motor nuclei and peripheral motor nerves underwent the least reductions in excitability in extreme acidosis. In the present experiments an attempt was made to study effects of acidosis on the cytologic structure of the nervous system with methods adequate to reveal slight changes in the structure of nerve cells of the brain.

## MATERIAL AND METHODS

Adult guinea pigs of both sexes and various ages were used. In one series of experiments acidosis was brought about by administering a 10 per cent solution of ammonium chloride by stomach tube in doses of 2 to 4 cc daily over varying periods. In other experiments acidosis was induced by venoclysis with a lactate buffer of  $p_H$  3.4 to 4.0 and by subjection of the animals to atmospheres of 30 per cent carbon dioxide in oxygen. The  $p_H$  of the blood was determined with a Coleman  $p_H$  meter on samples withdrawn under liquid petrolatum from the heart before the animals were killed. The animals were then anesthetized and fixed, in most instances while still alive, by perfusion with solutions of formaldehyde U S P (3-4) with acacia made isotonic with sodium chloride, according to the method previously described.<sup>2</sup> The brain was removed and placed in the fixing fluid for four or five days before it was embedded in a solution of pyroxylin of low viscosity, to be sectioned at 40 microns serially. Staining was done with the buffered thionine technic.<sup>3</sup> The histologic technic was carefully controlled by staining together sections of an experimental animal and similar sections of a control animal of like sex and weight.

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This study was aided by a grant from the National Foundation for Infantile Paralysis, Inc., to Northwestern University.

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2 Koenig, H., Groat, R. A., and Windle, W. F. A Physiological Approach to Perfusion-Fixation of Tissues with Formalin, *Stain Technol* **20** 13-22, 1945.

3 Windle, W. F., Rhines, R., and Rankin, J. A Nissl Method Using Buffered Solutions of Thionin, *Stain Technol* **18** 77-86, 1943.

## RESULTS

An attempt was first made to study possible effects of chronic acidosis on the structure of the brain. Twelve guinea pigs received daily doses of 10 per cent ammonium chloride by stomach tube for thirteen to thirty days. The  $p_H$  of the blood at the end of the experiment varied from 7.32 to 7.08, with a mean of 7.19, in contrast to the  $p_H$  of the blood of 9 normal guinea pigs, which varied from 7.55 to 7.30, with a mean of 7.43. The treated animals appeared to be entirely normal throughout the experiment, showing no neurologic signs and maintaining good health. Gross anatomic examination performed with the animal under pentobarbital anesthesia revealed no abnormalities. The brains of 7 of the guinea pigs were studied histologically, a careful comparison being made with sections of the brains of 2 control animals. No alterations in the structure of the brain could be observed in any of these animals. The sections were indistinguishable from the controls. A careful search through all the sections of the brains failed to reveal any intramedullary hemorrhages. Occasionally a few blood corpuscles were observed in the ventricles, but 1 of the control animals showed a similar phenomenon.

Fifteen other guinea pigs were rendered acidotic by forced feeding of a 10 per cent solution of ammonium chloride daily. Eight of these animals were fed the ammonium chloride simultaneously with the 12 in the preceding group. From a few hours to twenty-one days after the feeding of ammonium chloride was begun, in most instances as a result of a slight, and seemingly fortuitous, overdosage of ammonium chloride, the guinea pigs in this series were precipitated into a state of acute respiratory distress culminating in coma. The  $p_H$  values at this time varied from 6.70 to 7.25, with a mean of 7.01. The period of acute respiratory distress lasted from approximately five minutes (in 2 instances) to thirty minutes. Gross examination revealed a state of acute hemorrhagic pulmonary edema in all cases.

Histologic examination of the brains of the 11 animals studied revealed in each instance pathologic changes characteristic of asphyxia. Very small capillary hemorrhages were observed scattered through the brains of 7 of them. In some of these brains the hemorrhages were few and widely scattered. When the sections of the experimental brains were compared grossly with those of the control brains stained simultaneously, it was observed that the sections of 5 brains stained appreciably lighter than the controls. One other brain showed a slight difference. None of the control brains stained more lightly than its accompanying experimental brain. As observed microscopically, small regions around some of the capillaries, especially in the diencephalon, were pale and suggested

perivascular edema There was no sharp line of demarcation between the area of paling and the more darkly stained tissue Each of the experimental preparations could be distinguished from its control under the low power lens by the diffuseness of staining Nerve cells appeared to be less sharply defined than those of the control Critical examination of the larger neurons of the brain with a high power lens revealed a lack of sharpness in the staining of Nissl bodies This was most pronounced in the large interneurons, such as those of the red nucleus and the scattered large cells of the reticular formation of the medulla oblongata In the animals which had suffered the longest period of respiratory distress, many of the large interneurons were noticeably pale, and their Nissl bodies appeared to have undergone some dissolution

Although a pronounced acidosis existed in this second group of animals, there was no proof that the cytopathologic changes were caused by it Similar structural changes are seen in cases of asphyxia<sup>4</sup> Furthermore, asphyxia occurred with the pulmonary edema in the present experiments To clarify this relationship, 2 guinea pigs were subjected to rebreathing until they became dyspneic and entered a comatose state They were perfused while the hearts were beating, and the brains were studied histologically The brains resembled those of the animals in which pulmonary edema had developed after receiving large doses of ammonium chloride Structural alterations were of the same order

Chronic acidosis uncomplicated by pulmonary edema led to no demonstrable changes in structure of the brain An additional series of experiments was therefore performed in which severe acute acidosis without the pulmonary edema was produced by administration of a lactate buffer of  $p_H$  3.4 to 4.0 This buffer was administered by venoclysis In each instance a severe dyspnea developed This appeared to be different from the asphyxial gasping seen in the experiments with ammonium chloride Respiratory movements were regular, slow to rapid and deep, appearing to involve all the accessory muscles of respiration The animals were killed thirty minutes to one hour after administration of the buffer The vascular system was perfused with the fixing fluid, as in the other experiments At the time the 3 animals were killed the  $p_H$  of the blood was found to be 6.0, 6.45 and 6.55, respectively

The lungs exhibited no edema at autopsy Two of the 3 animals showed no intracranial hemorrhage, 1 had a small amount of blood around the brain stem and the cervical part of the spinal cord Histo-

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4 Windle, W. F., Becker, R. F., and Weil, A. Alterations in Brain Structure After Asphyxiation at Birth, *J Neuropath & Exper Neurol* 3:224-238, 1944

logic study was made of the brains of these 3 animals and of 1 control. No intramedullary hemorrhages were encountered, and no hemorrhages were found on the surface of 2 of the brains. In the other brain, the gross observation of hemorrhage around the brain stem was confirmed, and a considerable quantity of blood was noted in the cerebral aqueduct. There were no other intramedullary hemorrhages.

In spite of the severe acute acidosis produced in these animals and the presence of hemorrhage in the brain of 1, the nerve cells of the brain differed in no way from those in the control specimens. The depth of staining was equal to that of the control, and there appeared to be no dissolution of Nissl bodies anywhere. Thus, the brains of these animals were quite unlike the brains of the guinea pigs which had pulmonary edema after the administration of large doses of ammonium chloride.

Another experiment was performed in which severe acute acidosis was induced by breathing carbon dioxide. A chamber of 75 liter capacity was filled with a mixture of 30 per cent carbon dioxide and 70 per cent oxygen. Two adult male and 2 adult female guinea pigs were used in the experiment. Three normal controls were provided. At the end of five and one-half hours, during which time the gas flowed continuously into the tank, 2 animals were killed. The other 2 animals were killed after three hours in the tank. The  $p_{\text{H}}$  of the blood at the time the animals were killed ranged from 6.66 to 7.1, with a mean of 6.94. As in the preceding experiments, the animals were perfused first with an aqueous solution of acacia and sodium chloride ( $p_{\text{H}}$  4.55) and then with the fixing fluid, consisting of solution of formaldehyde U. S. P. (3.4) with acacia and sodium chloride ( $p_{\text{H}}$  4.32). The controls were similarly perfused.

No hemorrhages were observed at autopsy. The brains appeared to be normal in size and appearance. Histologic study revealed no intramedullary hemorrhages. The sections of the control brains stained a little more lightly than the simultaneously stained sections of the experimental brains. The darker staining of the brains of the animals which had been subjected to atmospheres rich in carbon dioxide was due to a more intense staining of the nerve elements themselves rather than to a difference in the staining of the neuroglia. It was not due to any difference in fixation or treatment of the histologic sections. The neurons were not more shrunken but simply took on more of the dye in the case of the experimental animals. The significance of this is not clear. It is a phenomenon not encountered in the other acidotic brains and is perhaps due to the carbon dioxide itself. It was entirely unlike the picture presented by the brains of asphyxiated animals.

## COMMENT

The results appear to be in sharp contrast to histopathologic changes in nerve tissue accompanying acidosis reported in the past. Thus, de Crinis<sup>5</sup> induced acidosis in rabbits and a dog over a period of three days or less by feeding and intravenous injection of sodium biphosphate (10 per cent solution). Among the cytologic changes reported were increase in glial cells, severely damaged ganglion cells and neuronophagia. He also observed these changes in the brains of patients, several of whom died of diabetic coma, several of eclampsia and several of status epilepticus, and he attributed the neurocytologic changes to the acidosis occurring in these conditions. Some of the alterations described in the human brains may well have occurred post mortem. Moreover, acidosis is but one of the disturbances in these clinical entities, and the pathologic changes described could be attributed to another factor. Preterminal asphyxia is capable of producing cytologic changes in the brain, as demonstrated in our present experiment. The changes described by de Crinis in the brains of the animals with experimentally induced acidosis are more difficult to explain. This investigator utilized 1 healthy rabbit as a control. He did not state how soon after death the animal brains were fixed. Thus, it is possible that some of the changes observed were in reality postmortem alterations. In our experiments, the animals were fixed while still biologically alive. Postmortem autolysis and other alterations were thus prevented.

Funagoshi, Chojā and Hayami<sup>6</sup> also reported histopathologic changes in the central nervous system occurring with experimental acidosis. These investigators induced acidosis in rabbits by the subcutaneous injection of hydrochloric acid and phosphoric acid. The cellular changes described included protoplasmic atrophy, pyknosis, atrophy, granulation, coalescence and disappearance of the Nissl bodies, pyknosis, swelling, increase in number, light staining and shrinkage of mitochondria. The mitochondria were not studied in our material, nevertheless, the other neuronal alterations reported by these men were not confirmed by our experiments. Here, too, the time interval between killing the animals and fixation was not reported, nor were control brains said to have been studied.

The absence of visible cytopathologic changes in the brain in experimental acidosis is consistent with the relatively slight effect acidosis is

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5 de Crinis, M. Ueber die Beeinflussung des histologischen Bildes des Zentralnervensystems durch humorale Veränderungen, *Monatschr f Psychiat u Neurol* 58 185-221, 1925

6 Funagoshi, M., Chojā, N., and Hayami, Y. Ueber die Veränderung der Mitochondria in den verschiedenen Ganglienzellen bei experimenteller Azidosis und Alkalosis, *Tr Soc path jap* 27 459, 1937

known to have on the electrical excitability of nerve cell bodies and nerve fibers as compared with its effect on spinal reflexes (Koenig and Groat<sup>1</sup>) The physicochemical alterations in the central nervous system consequent to acidosis are still but little known and are not necessarily reflected in structural change

#### SUMMARY

Guinea pigs were given a solution of ammonium chloride by stomach tube daily over varying periods to induce chronic acidosis No cytologic changes were observed in the brains Other animals were made acutely and extremely acidotic by administering a lactate buffer or by subjecting them to atmospheres of 30 per cent carbon dioxide in oxygen No structural changes could be seen in the nerve cells of the acidotic animals given the buffer solution, although the neurons of the animals breathing carbon dioxide stained appreciably darker than did those of the controls

When administration of ammonium chloride resulted in coma associated with acute hemorrhagic pulmonary edema, nerve cells of the brain exhibited pathologic alterations which were identifiable as phenomena of asphyxia

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# MENINGOENCEPHALITIS COMPLICATING HERPES ZOSTER OPHTHALMICUS AFTER TREATMENT BY VACCINATION

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SEVERAL investigators have given as explanation of the encephalitis following vaccination and the exanthems the theory of the activation of a latent virus by the vaccination or the exanthem. Van Bastiaanse and co-workers<sup>1</sup> expressed the opinion that the postvaccinal encephalitis occurring in the Netherlands was the result of rousing to active manifestation an encephalitis existing previously in the latent stage. They stated the belief that the virus involved was that of epidemic encephalitis. Netter,<sup>2</sup> Kraus,<sup>3</sup> Demme<sup>4</sup> and Pette<sup>5</sup> also favored this idea. The members of the Committee on Vaccination, Great Britain, with one exception, held this opinion, they stated in 1928.<sup>6</sup> "It is not altogether improbable that vaccination may here and there have precipitated an encephalitis in a person harbouring another virus." Ledingham<sup>7</sup> wrote

Till further notice I take the view that postvaccinal encephalitis is more probably the result of activation of some latent virus parasitising certain hosts and that it is on all fours with the similar syndromes following occasionally measles, chickenpox, etc.

Lust<sup>8</sup> also maintained that the encephalitis following measles was attributable not to the measles virus but to the awakening of a latent

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5 Pette, H. Das Problem der postvakzinalen Enzephalitis, München med Wchnschr **75** 207, 1928

6 Report of the Committee on Vaccination, Great Britain, Ministry of Health, London, His Majesty's Stationery Office, 1928

7 Ledingham, J C G. Studies on Virus Problems. I Tissue and Cell Affinities of Viruses and Reactions of the Host, Bull Johns Hopkins Hosp **56** 247, 1935

8 Lust, F. Die paramorbillöse Encephalitis und ihre Folgen, Monatschr f Kinderh **34** 284, 1926

neurotropic virus by the measles virus Schick<sup>9</sup> stated the opinion that measles lowered the resistance to attack and invasion by a neurotropic virus

Experimental studies on the activation of one virus by another are few, but Levaditi and Nicolau<sup>10</sup> observed in the rabbit that rabies produced by the injection of the virus of rabies can cause death from neurovaccinia which had been latent In later experiments<sup>11</sup> they claimed that the herpes virus when placed on the nasal mucosa of a rabbit is by the simultaneous inoculation of vaccine on the skin stimulated to produce a fatal herpetic encephalitis Zurukzoglu<sup>12</sup> inoculated 9 rabbits Three received 0.5 cc of herpes virus subcutaneously, followed a few minutes later by 0.2 cc of smallpox vaccine lymph intravenously Three rabbits received only the dose of herpes virus subcutaneously, while 3 received only the dose of vaccine intravenously The 6 control animals remained alive, whereas 2 of the animals which received both viruses died on the ninth and the thirteenth day, respectively, with clinical symptoms of herpetic encephalitis It is thus suggested that a sublethal dose of herpes virus given subcutaneously was induced to excite encephalitis by the simultaneous injection of smallpox vaccine Thomsen<sup>13</sup> found that the simultaneous inoculation into the skin of monkeys of the viruses of vaccine and poliomyelitis may induce the clinical picture of the latter disease, whereas the simple vaccination of the skin with poliomyelitis virus produced no effect of any kind In the explanation of recurrent fever blisters, Rivers<sup>14</sup> wrote that persons with this condition usually possess an abundance of antibodies against the active agent in their serums

The paradox has been explained on the basis of the persistence of the virus in the cells of immune individuals who develop crops of blisters whenever subjected to the conditions that are encountered as a result of typhoid vaccination, common colds, exposure to high temperatures for several hours, etc

In other words, the common cold, which is a virus infection, may activate the virus of herpes febrilis Fyfe and Fleming<sup>15</sup> reported 9 cases of

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9 Schick, in discussion on Lust<sup>8</sup>

10 Levaditi, C, and Nicolau, S Les associations entre ultravirus neurotropes, *Compt rend Soc de biol* **93** 3, 1925

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13 Thomsen, O Experimentelle Untersuchungen über die Poliomyelitis, *Ztschr f Immunitätsforsch u exper Therap* **14** 198, 1912

14 Rivers, T M Lane Medical Lectures Viruses and Virus Diseases, Stanford University, Calif, Stanford University Press, 1939, p 60

15 Fyfe, G M, and Fleming, J B Encephalomyelitis Following Vaccination in Fife, *Brit M J* **2** 671, 1943

encephalomyelitis following vaccination for smallpox in Fife, Scotland, where 75,326 vaccinations were performed recently, during an epidemic of smallpox. Patients 2, 3, 4 and 6 had acute pharyngitis, patient 7, rales in the chest, and patient 8, a history of recent laryngitis. The findings of these authors suggested, at least, that the hazard of encephalitis during vaccination is much greater when there is concomitant infection in the upper respiratory tract. It is not unreasonable to postulate that several of the infections in these patients were due to viruses.

The following report concerns a case of herpes zoster ophthalmicus in which meningoencephalitis developed subsequent to vaccination employed as treatment for the herpes.

#### REPORT OF A CASE

*History*—A white man aged 60 was admitted to the hospital on Nov 7, 1945, with coma of several hours' duration. Previous illnesses included pneumonia and bronchitis in 1940 and typhoid in youth. He was married and had 5 children, 1 son was epileptic. He had been vaccinated twice in early life. He was well and working up to Oct 26, 1945, when he complained of pain in the left frontal area. On the following day his left eye became inflamed. On October 28 a vesicular eruption appeared on the left side of the nose and forehead, the next day the rash had spread. He was vaccinated on October 30, in treatment of the herpes. Except for pain in the frontal region and eye, he was well until November 7. That morning he was awakened with great difficulty and remained awake only long enough to make some unintelligible sounds. Later his extremities became "stiff" and the family noticed occasional movements of the limbs.

*Examination*—On his admission, the temperature was 99.4 F, the blood pressure was 140 millimeters of mercury systolic and 75 millimeters diastolic, and the pulse rate was 80 per minute. There were vesicular lesions, many of them crusted, on the left side of the nose and the left supraorbital region. Two old vaccination scars and a recent vaccination scab was present on the left arm. He was comatose and could not be roused by supraorbital pressure. Tonus in the limbs frequently varied from hypertonicity to flaccidity. At times the lower limbs could not be flexed, even with force. Cogwheel rigidity was elicited at the elbows. There was hyperreflexia in the upper limbs. The Gordon and Mendel-Bechterew signs, a defective plantar response and diminished abdominal reflexes were demonstrated on the left side. Nuchal rigidity was pronounced. The pupils were small, the right pupil reacted to light but not the left. The conjunctiva of the left eye was diffusely reddened and edematous, the cornea was cloudy as a result of posterior precipitates and folds in Descemet's membrane. Fine tremors of the lower jaw were noted from time to time.

*Laboratory Data*—The blood count showed 5,500,000 erythrocytes, 100 per cent hemoglobin, and 14,600 leukocytes, with 86 per cent polymorphonuclear leukocytes, 13 per cent lymphocytes and 1 per cent monocytes. The Kahn test of the blood was negative. Urea nitrogen was 16 mg, and the blood sugar 69 mg, per hundred cubic centimeters. The urine was normal. Lumbar puncture on November 7 revealed a clear, colorless fluid with an initial pressure of 120 mm of water, a cell count of 100 lymphocytes per cubic millimeter, a positive Pandy reaction, a total protein of 120 mg per hundred cubic centimeters, a colloidal gold curve of 0033220000 and a negative Wassermann reaction. Culture of the spinal fluid disclosed no bacteria.

*Course of Illness*—The patient remained in coma for forty-eight hours and then began to respond. On November 9 he was confused as to his age. He thought he was dead and in a morgue and that the examiner was an undertaker. He was extremely suspicious and was slow in responding to questions. There was definite impairment of memory for both recent and remote events. He could not state where he was or give the approximate month or year, he could not name his children. There was no confabulation. The Gordon sign on the left and the nuchal rigidity were still present. The temperature rose on November 8 to 102 F and fluctuated between 99 and 101 F, until it dropped to normal on November 20. The patient's mental state gradually returned to normal, and on November 27 he was fully alert, cooperative and oriented. There were no delusions or hallucinations. He answered questions briskly, and the family was of the opinion that he was back to his usual state. The cutaneous lesions had practically disappeared by November 23. Lumbar puncture was repeated on November 27. The fluid was clear, the initial pressure was 150 mm of water, there were 66 lymphocytes per cubic millimeter, the sugar was 52.6 mg, and the total protein 138 mg, per hundred cubic centimeters. Another examination of the spinal fluid was done on December 4 and disclosed clear fluid, with initial pressure of 160 mm of water, 30 lymphocytes per cubic millimeter and a total protein of 75.5 mg per hundred cubic centimeters. On December 17 the final spinal puncture showed clear fluid, 50 lymphocytes per cubic millimeter and a total protein of 64 mg per hundred cubic centimeters.

During his hospitalization the patient received 280,000 units of penicillin and was given 14 Gm of sulfadiazine between November 7 and November 9. No objective signs of focal involvement of the central or the peripheral nervous system were present on his discharge, on December 30.

#### COMMENT

The subject of this report had no clinical indications of meningoencephalitis until eight days after vaccination. Lillie<sup>16</sup> suggested lymph vaccination as a treatment for herpes zoster ophthalmicus, and he employed it in 11 cases with success. However, in his first case meningoencephalitis developed ten months after the vaccination. He stated

The meningoencephalitis might be of virus origin but I feel that the infection of the skin of the nose was the more probable cause of the condition.

The patient recovered.

Alterations in the cerebrospinal fluid in patients with herpes zoster are found even though no clinical signs of meningoencephalitis are demonstrable. Lymphocytosis is reported in many instances<sup>17</sup>. Achard,

16 Lillie, W. I. The Treatment of Herpes Zoster Ophthalmicus with Smallpox Vaccine, New York State J. Med. **43** 857, 1943.

17 Chauffard, A., and From, G. Nature, evolution et durée de la réaction méningée dans le zona, Bull. et mém. Soc. méd. d'hôp. de Paris **19** 994, 1902. Chauffard, A., and Rendu, H. Méningite zonateuse tardive dans un cas de zona ophtalmique, *ibid.* **24** 141, 1907. Brissaud and Sicard. Cytologie du liquide céphalo-rachidien au cours du zona thoracique, *ibid.* **18** 260, 1901. Wiegmann, F. Herpes zoster cephalicus (20 eigene Beobachtungen), München med. Wchnschr. **81** 1970, 1934.

Loeper and Laubry<sup>18</sup> noted lymphocytosis in 50 per cent of 16 cases. Brown and Dujardin<sup>19</sup> reported lymphocytosis in 28 of 42 cases, and they stated the opinion that the presence of syphilis was not a factor. Schussler<sup>20</sup> found an increase of cells in 16 of 18 cases. Touraine<sup>21</sup> noted pleocytosis in 50 per cent of 97 cases of localized herpes zoster collected from the literature or occurring in his own experience. In a similar percentage of cases of generalized herpes zoster, the cells were increased.<sup>22</sup> Henkel<sup>23</sup> reported an increase of cells in 19 of 30 cases of idiopathic herpes zoster and an elevated protein content in 40.3 per cent of 57 cases. Merritt and Fremont-Smith<sup>24</sup> examined the fluid in 8 cases and found an increase in the number of cells in 6 of them. The pleocytosis may persist for a long time,<sup>25</sup> even as long as two or three weeks after healing of the herpes.<sup>26</sup> Sicard<sup>27</sup> reported 2 cases in which the spinal fluid had an increased cellular content ten and thirteen months, respectively, after the appearance of the eruption.

Occasionally a full blown meningoencephalitis develops in a case of herpes zoster. Krumholz and Luhan<sup>28</sup> described the autopsy in such a case and briefly summarized 5 others collected from the literature. They mentioned 3 other cases in which no autopsy was performed.

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18 Achard, C., Loeper, M., and Laubry, C. *Le liquide cephalo-rachidien dans le zona*, Bull et mem Soc med d hôp de Paris **18** 985, 1901.

19 Brown, W. H., and Dujardin, B. *The Cerebrospinal Fluid in Herpes Zoster, and the Relation of Herpes Zoster to Syphilis*, Brain **42** 86, 1919.

20 Schussler, D. *Ueber die Liquorveränderungen beim Zoster*, Dermat Wchnschr **100** 381, 1935.

21 Touraine, A. *Zona et liquide cephalo-rachidien*, Ann de dermat et syph **6** 289, 1935.

22 Touraine, A. *Le liquide cephalo-rachidien dans les zonas generalises*, Bull Soc franç de dermat et syph **42** 500, 1935.

23 Henkel, T. *Liquor und Herpes Zoster*, Thesis, Köln, 1935, Köln, J. Borowsky, 1936.

24 Merritt, H. H., and Fremont-Smith, F. *The Cerebrospinal Fluid*, Philadelphia, W. B. Saunders Company, 1938, p. 137.

25 Touraine, A., and Baumgartner, P. *Zona ophtalmique double*, Bull Soc franç de dermat et syph **41** 736, 1934. Jacquet, P., and Bariety, M. *Zona ophtalmique oculo-sympathique, valeur de l'épreuve des collyres*, Bull et mem Soc med d hôp de Paris **50** 1561, 1926. Henkel<sup>23</sup>.

26 (a) Georgi, F., and Fischer, O. *Humoralpathologie der Nervenkrankheiten*, in Bumke, O., and Foerster, O. *Handbuch der Neurologie*, Berlin, Julius Springer, 1935, vol. 7, pt. 1. (b) Gordon, I. R. S., and Tucker, S. F. *Lesions of the Central Nervous System in Herpes Zoster*, J. Neurol, Neurosurg & Psychiat **8** 40, 1945. (c) Denny-Brown, D., Adams, R. D., and Fitzgerald, P. J. *Pathologic Features of Herpes Zoster*, Arch Neurol & Psychiat **51** 216 (March) 1944.

27 Sicard, J. A. *Le liquide cephalo-rachidien*, Paris, Masson & Cie, 1902, p. 182.

28 Krumholz, S., and Luhan, J. A. *Encephalitis Associated with Herpes Zoster. Report of a Case*, Arch Neurol & Psychiat **53** 59 (Jan.) 1945.

The cellular changes in the spinal fluid associated with postvaccinal encephalitis are much less frequent, and they remain abnormal for a much shorter period. The spinal fluid in the 34 cases of van Bastiaanse<sup>1</sup> was normal except for slight pleocytosis in a few instances. There were no abnormalities in the fluid in the 3 cases of Lucksch<sup>29</sup>. Lerner<sup>30</sup> reported 3 cases. The highest cell count was 181 cells per cubic millimeter fourteen days after vaccination, six days later it dropped to 10 cells per cubic millimeter. In a second case the cells decreased from 18 to 9 per cubic millimeter in eleven days. Frommel and Baumgartner<sup>31</sup> found 121 cells per cubic millimeter, with 88 per cent polymorphonuclear leukocytes, twelve and a half days after vaccination in a case of postvaccinal encephalitis. On the following day the cell count had dropped to 71 per cubic millimeter, with 86 per cent polymorphonuclear leukocytes. Rietschel's<sup>32</sup> patient had 70 cells per cubic millimeter of spinal fluid fourteen days after vaccination. In Roper's<sup>33</sup> case there were 118 cells per cubic millimeter with 82 per cent lymphocytes, and a total protein of 90 mg per hundred cubic centimeters fifteen days after vaccination. Two weeks later there were only 14 lymphocytes per cubic millimeter and a protein content of 35 mg per one hundred cubic centimeters. In the report of the Committee on Vaccination of 1930,<sup>34</sup> there were increased white cells in 8 of 19 fatal cases, with 1 exception, the count was below 50.

In the cases of Coyle and Hurst<sup>35</sup> and Horder<sup>36</sup> no increase in cells or protein was present thirteen and twelve days respectively, after vaccination. Taylor's<sup>37</sup> patient had an "excess of leukocytes, not marked." There was no elevation in the globulin. Flexner's<sup>37a</sup> patient had 13

29 Lucksch, F. Gibt es beim Menschen eine Vakzine-Encephalitis? *Centralbl f Bakt (Abt 1)* **96**:309, 1925.

30 Lerner, C. Ueber zerebrale Krankheitserscheinungen im Verlaufe der Kuhpockenimpfung, *Med Klin* **22**:441, 1926.

31 Frommel, E., and Baumgartner, J. Accidents nerveux consécutifs à la vaccination antivariolique, *Schweiz med Wchnschr* **56**:857, 1926.

32 Rietschel, H. Ueber Encephalitis postvaccinalis mit Krankendemonstration, *Verhandl d phys-med Gesellsch* **56**:99, 1931.

33 Roper, F. A. Encephalitis Following Vaccination with Recovery, *Brit M J* **2**:103, 1933.

34 Vaccination. Further Report of the Committee, Great Britain, Ministry of Health, London, His Majesty's Stationery Office, 1930.

35 Coyle, C. D., and Hurst, E. W. Acute Disseminated Encephalomyelitis Following Vaccination, *Lancet* **2**:1246, 1929.

36 Horder, T. A Case of Cerebral Symptoms Following Vaccination, *Lancet* **1**:1301, 1929.

37 Taylor, J. F. A Fatal Case of "Post-Vaccinal" Encephalitis, *Lancet* **1**:1302, 1929.

37a Flexner, S. Postvaccinal Encephalitis and Allied Conditions, *J A M A* **94**:305 (Feb 1) 1930.

cells per cubic millimeter fifteen days after vaccination, and Miller's<sup>37b</sup> patient had 2 cells five days after vaccination, both patients died. Neal,<sup>38</sup> with personal experience of 10 cases, stated that "changes in spinal fluid are usually not marked and normal fluids may be found." Demme<sup>39</sup> also stated that in cases of postvaccinal encephalitis the spinal fluid is normal. In Facey's<sup>40</sup> case encephalitis and a cutaneous eruption developed one month after vaccination. Three examinations of the spinal fluid disclosed no abnormalities.

The patient described in this paper had herpes zoster ophthalmicus, with the probable presence of the herpes virus in the nervous system. As already indicated, in approximately 50 per cent of the cases of herpes zoster there are changes in the spinal fluid without demonstrable clinical signs of meningoencephalitis. The patient was vaccinated as a therapeutic measure, and the second virus apparently activated the latent herpes zoster into full blown meningoencephalitis. It may be argued that the meningoencephalitis was the result of vaccination. There are several points of evidence against this view. Postvaccinal encephalitis follows primary vaccination in the great majority of cases. In the report of the committee on vaccination of 1930,<sup>34</sup> 83 of 90 cases occurred in infancy after primary vaccination. In the present case the vaccination was the patient's third. The age of the oldest person reported by the Committee on Vaccinations in 1928 was 55<sup>o</sup>, the subject of the present study was 60. The persistence of alterations in the spinal fluid forty days after the initial puncture is also in favor of a herpes infection. Whether this patient would have had meningoencephalitis as a complication of the herpes zoster if he had not been vaccinated is difficult to say. In the majority of cases such a complication appears a little later in the course of the illness. However, one cannot ignore the probable role of the vaccination as a precipitating factor. Localized herpes zoster following vaccination has been noted.<sup>41</sup> Unfortunately, I was not able to conduct animal experiments with the spinal fluid. Even if the animals inoculated were to show histologic changes, it would not necessarily prove that vaccination produced the clinical picture in the patient, since the virus of vaccinia is occasionally present in the blood, in various organs and even in the spinal fluid in cases of severe reactions to vaccination without

37b Miller, M. K. Four Types of Encephalitis, *J. A. M. A.* **97** 161 (July 18) 1931.

38 Neal, J. B. Encephalitis, New York, Grune & Stratton, Inc., 1942, p. 104.

39 Demme, H. Liquorbefunde bei akuten Infektionen des Nervensystems, *Zentralbl. f. d. ges. Neurol. u. Psychiat.* **54** 133, 1930.

40 Facey, R. V. Encephalitis with Skin Eruption After Vaccination, *Lancet* **2** 669, 1942.

41 Dumont, J. Vaccine et zona, *Bull. et mém. Soc. méd. d. hôp. de Paris* **46** 1036, 1922. Frommel and Baumgartner<sup>31</sup>

complications<sup>12</sup> In addition, several investigators<sup>43</sup> found that the virus of vaccinal encephalitis, as well as the herpes zoster virus, could not be transmitted to animals

#### SUMMARY

An instance of meningoencephalitis with recovery in a 60 year old patient with herpes zoster ophthalmicus is reported The onset of the nervous complications appeared eight days after the patient was vaccinated in treatment for the herpes It would seem that the herpes virus was activated into a full blown meningoencephalitis by the vaccinia virus The persistence for weeks after the onset of changes in the spinal fluid occurring with meningoencephalitis complicating herpes zoster is confirmed in this case

1882 Grand Concourse (57)

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42 Herzberg-Kremmer, H, and Herzberg, K Untersuchungen über post-vakzinale Enzephalitis, Zentralbl f Bakt (Abt 1) **119** 175, 1930

43 Marinesco, G Contribution à la pathogénie et à la physiologie pathologique du zona zoster, Bull Acad de méd, Paris **88** 487, 1922 Blanc, G, and Caminopetros, J Contribution à l'étude expérimentale de zona, Bull Soc franç de dermat et syph **29** 294, 1922 Marinesco, G, and Draganesco, S Contribution à la pathogénie et à la physiologie pathologique du zona zoster, Rev neurol **39** 30, 1923 Doerr, R Ergebnisse der neueren experimentellen Forschungen über die Ätiologie der Herpes simplex und des Zoster, Zentralbl f Haut- u Geschlechtskr **16** 481, 1925 Cole, R, and Kuttner, A G The Problem of the Etiology of Herpes Zoster, J Exper Med **42** 799, 1925 Gordon, M H, cited in the Report of the Committee on Vaccination<sup>6</sup> Esser, A Die Hirnschädigungen nach Pockenschutzimpfung, Virchows Arch f path Anat **278** 200, 1930 van Bastiaanse and others<sup>1</sup> Kraus<sup>3</sup> Denny-Brown, Adams and Fitzgerald<sup>20c</sup>



## SURGICAL TREATMENT OF SYRINGOBULBIA AND SYRINGOPONTIA

Report of Two Cases

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**S**URGICAL operation on the brain stem for the relief of syringobulbia and syringopontia is herewith reported in 2 cases, with successful outcome. In a search of the literature I was unable to find reports of or references to precedence in the direct surgical attack on this entity. Its counterpart in the spinal cord, syringomyelia, has been successfully treated and reported on by a number of authors.

Frequently called the Puussepp procedure, the operation for syringomyelia was performed by Elsberg<sup>1</sup> at an earlier date and Abbe and Coley were credited by Adelstein<sup>2</sup> with the first report of this procedure, in 1892. Adelstein, Frazier,<sup>3</sup> Putnam,<sup>4</sup> Kuhlendahl,<sup>5</sup> Cox,<sup>6</sup> Worster-Drought and associates,<sup>7</sup> Woods and Pimenta<sup>8</sup> and others cited by them have all reported on the surgical treatment of syringomyelia. Whereas Frazier,<sup>9</sup> in evaluating 2 of his own cases and 14 early cases collected from the literature, found notable improvement in 50 per cent, Woods and Pimenta,<sup>8</sup> in 1944, in an analysis of the 20 cases which they reported, averred that the surgical treatment of syringomyelia, with or without roentgen therapy, has not produced the hopeful results previously reported in the literature. It should be emphasized, as several of these

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1 Elsberg, C. A. Surgery of Intramedullary Affections of the Spinal Cord. Anatomic Basis and Technic, *J. A. M. A.* **59** 1532-1536 (Oct 26) 1912.

2 Adelstein, L. J. The Surgical Treatment of Syringomyelia, *Am. J. Surg.* **40** 384-395 (May) 1938.

3 Frazier, C. H. Drainage of a Syringomyelic Cavity, Twice in the Same Patient, Three Years Intervening, *J. A. M. A.* **101** 1228 (Oct 14) 1933.

4 Putnam, T. J. Syringomyelia. Diagnosis and Treatment, *M. Clin. North America* **19** 1571-1582 (March) 1936.

5 Kuhlendahl, H. Die operative Beeinflussbarkeit der Hydromyelia und Syringomyelia, *Deutsche Ztschr. f. Nervenheilk.* **140** 1-27 (Feb 22) 1936.

6 Cox, L. B. On the Origin and Treatment of Syringomyelic Cavities, *M. J. Australia* **1** 481-483 (March 12) 1938.

7 Worster-Drought, C., Wakeley, C. O. G., and Shafar, J. The Surgical Treatment of Syringomyelia, *Brit. J. Surg.* **29** 56-73 (July) 1941.

8 Woods, W. W., and Pimenta, A. M. Intramedullary Lesions of the Spinal Cord. Study of Sixty-Eight Consecutive Cases, *Arch. Neurol. & Psychiat.* **52** 383-399 (Nov.) 1944.

9 Frazier, C. H., and Rowe, S. The Surgical Treatment of Syringomyelia, *Ann. Surg.* **103** 481-497 (April) 1936.

authors have already done, that the indications for operation should be those already well established for operation on the central nervous system. In the case of syringomyelia the most important indication is a relentless progression of symptoms, coupled with evidences of abnormal tension and of cerebrospinal fluid block and correct localization. If these criteria are applicable to syringobulbia, the operation may be urged. Certain reservations, based on the disseminated and progressive nature of the basic pathologic state, must be borne in mind. It must be realized that many of the symptoms will, of necessity, remain static because of the essentially destructive nature of the disease. However, the signs and symptoms of increasing pressure will be relieved, and if the end stage of cavity formation has been reached at the time of operation the further progress of the disease may be halted. Furthermore, not all the paralytic symptoms are necessarily due to irreversible changes in the cellular groups and neural pathways involved. Some may be produced merely by direct hydrostatic pressure from the adjacent cavity and after relief of this tension may show improvement.

#### REPORT OF CASES

CASE 1<sup>10</sup>—A 35 year old timekeeper and clerk was treated in the Neurological Institute of New York from July 17 until Sept 16, 1941, with craniectomy in the posterior fossa on Aug 21, 1941. He entered the hospital with the following chief complaints: (1) Blurred vision, later becoming true diplopia, of sudden onset, in the summer of 1939, while he was reaching to catch a ball during a game. The disturbance recurred intermittently, chiefly on movements of the head, and had a progressive course. (2) Awkwardness of the left hand, first noted in typewriting in the late summer of 1939, and later, in more pronounced form, in piano playing, in the autumn of 1939. (3) Attacks of light headedness and sensations of being suspended in air, accompanied with diplopia and precipitated by looking to the left; onset in the winter of 1939. (4) Staggering gait and tendency to drag the left foot, onset in the spring of 1941. (5) Tinnitus, bilateral, occurring spontaneously at times but chiefly on turning the head sharply, onset in the spring of 1941. (6) Coarse tremor of the left forearm, of pronation-supination type, occurring frequently, on attempting purposive movements, onset in the summer of 1941. (7) Nuchal pain and headache, radiating from the base of the skull, posteriorly, up over the vertex in the midline. This occurred chiefly on flexion of the head, as when he was lacing his shoes, it also was noted on extension of the head and on coughing, sneezing and straining at stool. Onset was in the summer of 1941. (8) Nausea and vomiting, occasional, sometimes projectile, preceding his admission to the hospital.

The past history was not remarkable except for a chronic cough of twelve years' duration, diagnosed as bronchiectasis and productive of a few teaspoons of pus daily, which was not foul tasting or malodorous. He also had had two head traumas. The first had occurred twenty years before and was associated with retrograde amnesia but not unconsciousness, the second, occurring after the onset of his present illness, the result of tripping on the stairs, was associated with

<sup>10</sup> Case 1 is from the Department of Neurology, Columbia University College of Physicians and Surgeons, and the Neurological Institute of New York.

bleeding from the ear, ecchymosis about the eyes and a state of being dazed, without unconsciousness

*General Physical Examination*—The patient was slender and prematurely gray, he did not appear acutely ill on admission but grew progressively worse during the period of preoperative observation in the neurologic and neurosurgical services. The general physical condition was normal.

*Neurologic Examination*—*Gait* He walked with a broad base and showed a tendency to stagger in either direction and to veer toward the right. No hemiplegic attitude was obvious, but the associated swing of the left arm in walking was diminished, and in crawling he tended to slide the left hand forward instead of lifting it, as he did the right.

*Motor Status* Motor power was reduced in both left extremities, yet he was able to walk on both his heels and his toes. Equilibration was normal. Non-equilibratory coordination tests revealed a tremor of the left forearm in both pronation and supination, this occurred intermittently when the patient was at rest or was leaning on his palm. Succession movements were poorly performed in both left extremities, there was past pointing in the left hand, and check and rebound phenomena were abnormal in the left arm. Posture holding was normal.

*Reflexes* The tendon reflexes were hyperactive throughout but were more exaggerated on the left. The superficial reflexes were all present and equal, except that the plantar response on the right was not as definite as that on the left.

*Cranial Nerves*—*First* The olfactory nerves were normal.

*Second* Visual acuity and the visual fields were normal on gross testing. The vessels were normal, but the edges of the disks were blurred on the nasal side.

*Third, Fourth and Sixth* There was pronounced, sustained nystagmus on looking toward the left, and some on lateral gaze to the right. There was slight ptosis of the left upper eyelid. The right pupil was 5 mm larger than the left.

*Fifth* Sensation was normal over the face. Some equivocal sensory alteration was noted on the anterior portion of the left side of the tongue. The corneal reflex was decreased in strength on the left side, the loss developing during the period of observation. The masseter and temporal muscles were paralyzed on the left side.

*Seventh* There was weakness in all the muscles of expression on the left side of the face. The greatest weakness was in the lower portion of the face, simulating facial paresis of central origin except that spontaneous blinking was also affected.

*Eighth* Hearing was normal except for audiometric diminution in the upper tones in both ears. Responses to the caloric test were not determined.

*Ninth and Tenth* There was no gross loss of function, but the pharyngeal and palatal reflexes lagged on the left side.

*Eleventh* No weakness was demonstrable in the sternocleidomastoid or the trapezius muscles, yet the patient held the head rotated toward the left, with the chin elevated.

*Twelfth* The tongue deviated slightly toward the left.

*Mental State*—The mental condition of the patient was normal.

*Special Studies*—Roentgenographic examination of the chest revealed nothing abnormal. Roentgenograms of the skull revealed no evidences of increased intracranial pressure and no abnormalities of the sphenoid or petrous ridges or of the internal acoustic meatuses.

Electroencephalographic studies revealed no abnormalities of focal nature, but there was a diffuse mild abnormality. Phase reversal was noted in both frontal regions, and there was low voltage, fast and slow activity, throughout.

Pneumoencephalographic examination was performed on Aug 17, 1941, 80 cc of fluid being replaced with 75 cc of air. The lateral and third ventricles were moderately dilated, the cisterna pontis was narrowed, and the anterior extension of the left cisterna magna was narrowed, while only the posterior portion of the cistern on the right was visualized. The roentgenographic diagnostic impression was that of tumor in the posterior fossa, in the cerebellum rather than in the brain stem, and to the right of the midline.

Routine laboratory tests of the blood and urine revealed no abnormality. The protein of the cerebrospinal fluid measured 60 mg per hundred cubic centimeters.

The preoperative clinical diagnosis was tumor of the brain stem, probably glioma, with an extra-axial growth, possibly meningioma, a less likely probability. Because of the relentless progression of his symptoms and beginning deterioration of his general status, operation was advised.

*Operation*—On August 21, with the use of local anesthesia and with the patient in the sitting position, a craniectomy was carried out in the posterior fossa. On opening the dura, the cerebellar tonsils were noted to be herniated into the spinal canal to a considerable extent. Exploration was first carried out in the left cerebellopontile angle, where, at the point of emergence of the trigeminal nerve, an abnormal protuberance of the brain stem was encountered. Its thin wall was opened by blunt dissection, and an unmeasured quantity of yellow fluid escaped. No tumor tissue was observed. The depth of the remaining cavity was about 1 cm. The interior of the fourth ventricle was then explored, and the left half of the floor of the ventricle was observed to be tumefied and greatly deformed. Just above the acoustic striae there was an obviously thin-walled cyst, which was entered by blunt dissection and evacuated of its yellow fluid contents. The size of the cavity was not accurately determined. A specimen of the wall was removed for histologic examination. The maneuvers described had no appreciable effect on the patient's vital condition or immediate symptoms.

*Pathologic Report on Surgical Specimen* (Dr. Abner Wolf)—Gross Examination. The specimen consisted of two small pieces of tissue, measuring 7 by 5 by 4 mm and 4 by 5 by 6 mm respectively, which had the consistency of soft rubber. The tissue was pale gray, and the outer surface was smooth and uniform in appearance.

*Microscopic Study*. The specimen consisted of a number of fragments of neural tissue. Some of these contained clusters of nerve cells and tracts the architectural arrangement of which suggested that of the normal brain stem. Others contained no nerve cells or only a few sclerotic cells. In these areas there appeared to be an increase in glial fibers, and there were homogeneous, twisted fragments of deeply-staining reddish material, the so-called Rosenthal fibers. Occasional perivascular lymphocytic infiltrations were seen in such zones. On the surface of some of these areas were what appeared to be flattened ependymal cells. This tissue at times appeared to be rather edematous. No tumor tissue was noted in the specimen. The dense mass of glial tissue, the Rosenthal fibers and the adjacent, well preserved parenchyma of the brain stem suggested that the specimen was from the wall of a syrinx.

The pathologic diagnosis was syringopontia. There was no gross or microscopic evidence of tumor (fig 1).

*Postoperative Course*—The patient's complaints referable to increased intracranial pressure were relieved by the operation, and he made an uneventful recovery from the procedure. Postoperatively, there was a coarser and more frequent tremor of the left arm and no appreciable change in the symptoms of cranial nerve palsy,

and the ataxia remained. Six months after operation, on a follow-up visit to the clinic the patient was ambulatory but was still very ataxic. He was last observed, for the purpose of this report, fourteen months after operation, at which time he was not yet employed but was seeking work consistent with his status, to which he was becoming accustomed. He still retained, however, the neurologic deficits which he had before operation.

**CASE 2**—The 35 year old widow of a deceased Army officer entered an Army general hospital on Aug. 8, 1943, with the following chief complaint. At intervals for many years she had had a peculiar, shocklike sensation referable to the atlanto-occipital region. This had occurred particularly on movement of the head and was a distressing sensation. The same movement precipitated a similar shocklike sensation in the lower extremities. Until about June 1943 she had had these sensations intermittently, during self-limited periods. However, for the several

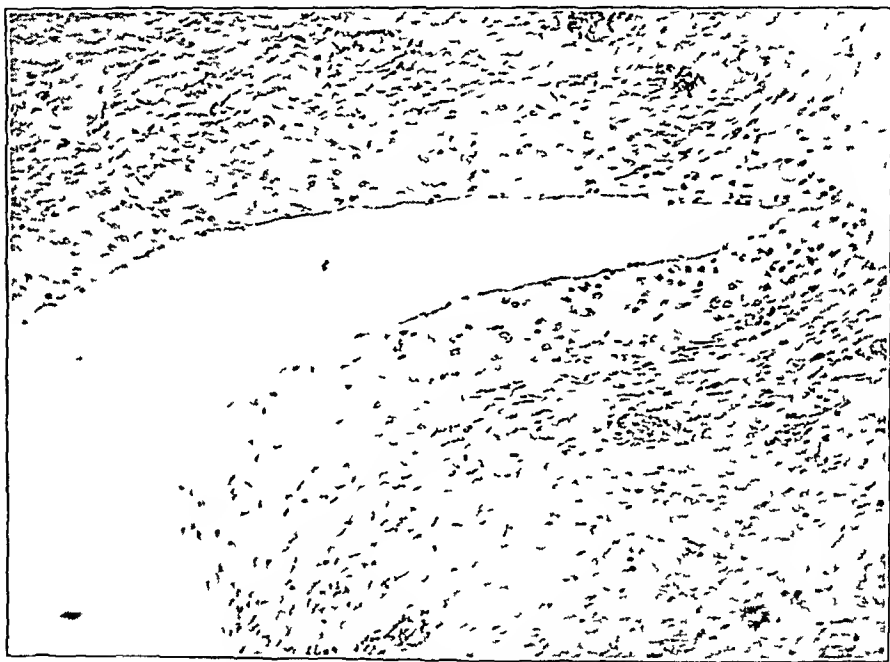


Fig. 1 (case 1) —Section from the wall of the cavity in a case of syringomyelia

weeks before her admission to the hospital they had become severe and persistent and had been associated with the following complaints: (1) pain in both upper extremities, chiefly on the right, (2) subjective numbness on the right side of the face and tongue, (3) a subjective sensation of weakness in the throat, making breathing difficult, (4) a disturbance in salivation, which she referred to the right side, under the tongue and described as "tangy" or "cankery", (5) a tingling sensation on the right side of the tongue, (6) nausea and vomiting, and (8) blurred vision.

**Neurologic Examination**—Gait. The gait was moderately ataxic, and she was unsteady in standing on either foot alone or on both feet together with the eyes open or closed.

**Motor Status**. There was no gross loss of motor function.

**Reflexes**. There was moderate hyperreflexia over the entire right side.

**Sensation** There was slight diminution of sensation to all modalities over the right side of the forehead and the bridge of the nose. There was also some sensory diminution on the right half of the face and tongue, on the right posterior wall of the pharynx and of the palate and on the left side of the trunk and the left extremities.

**Cranial Nerves**—**First** No subjective, or objective loss of olfactory sense was apparent.

**Second** There was no definite papilledema, but the veins were dilated in both fundi, particularly in the upper portion of the right and the lower portion of the left.

**Third, Fourth and Sixth** There was subjective blurring of vision. No weakness of the ocular muscles was apparent, but a fine, rhythmic nystagmus appeared on lateral gaze to either side and on looking upward.

**Fifth** The motor portion of the nerve was normal, sensation in the distribution of this nerve has been described in the preceding section.

**Seventh** The seventh nerve was normal.

**Eighth** Hearing was 20/20 bilaterally. The caloric test with injection of ice water into each ear produced nystagmus in twenty seconds of one hundred and fifty seconds' duration. This response was interpreted by the otologist as showing a hyperirritable labyrinth.

**Ninth and Tenth** There were subjective disturbance of salivation, as noted previously, and diminished sensation over the pharynx and palate. Speech was abnormal, being "palatal," but there was no hoarseness or paralysis of the palate, and the uvula moved in the midline.

**Eleventh** The nerve was normal.

**Twelfth** There were slight, but definite, atrophy of the lateral border of the right side of the tongue and deviation of the tongue toward the right on extension.

**Laboratory Data**—The blood and urine were normal. Examination of the spinal fluid showed no trace of globulin, but the total protein was increased to 52 mg per hundred cubic centimeters. There were 2 white cells per cubic millimeter, these were lymphocytes. The colloidal gold curve was 1111100000.

**Preoperative Diagnosis**—The diagnostic probabilities were (1) tumor, (2) syringobulbia and (3) adhesive arachnoiditis.

**Clinical Course**—Under observation, the patient grew progressively worse, complaining of nausea, vomiting and headaches, which were nuchal and occipital. Her condition began to become alarming, and inasmuch as the neurologic picture was patent in its localization of the lesion in the medulla, an exploratory operation was decided on.

**Operation**—On October 1, with the patient under ether anesthesia, an upper cervical laminectomy and a suboccipital craniectomy on the right side, extending across the midline, were performed. When the dura was opened, a large cyst was disclosed, occupying the upper segment of the cervical part of the cord and the medulla and filling the entire space usually occupied by the cisterna magna and the inferior portion of the fourth ventricle. This cyst was overlaid with a somewhat thickened and vascularized arachnoid membrane. At the lateral extent of the cisterna cerebellomedullaris there was a small cistern containing clear fluid. The dura was held in retraction by silk sutures, and the cystic mass was then explored. It was observed to extend from the spinal cord opposite the junction of the first and second cervical laminae into the fourth ventricle. It had displaced both cerebellar hemispheres upward and laterally, hollowing out a large space.

between them. There were small blood vessels coursing over the surface of this cystic mass. It was incised in an avascular area and approximately 30 cc of yellow cystic fluid aspirated. Some of this was sent to the laboratory for examination. Within this cystic cavity, the roof of which was opened widely with a longitudinal incision, no tumor tissue could be seen. The walls were of a yellowish appearance. At the inferior portion of the cyst, where it joined the body of the medulla, there were several large veins. With the deflation of the cyst it was seen that the upper portion, which filled the fourth ventricle, was merely the wall. The lower portion, at the junction of the medulla and the spinal cord, was solid. This portion was rather vascular. A small section of the wall of the cyst was removed for examination. After evacuation of the cyst, the dura was closed with

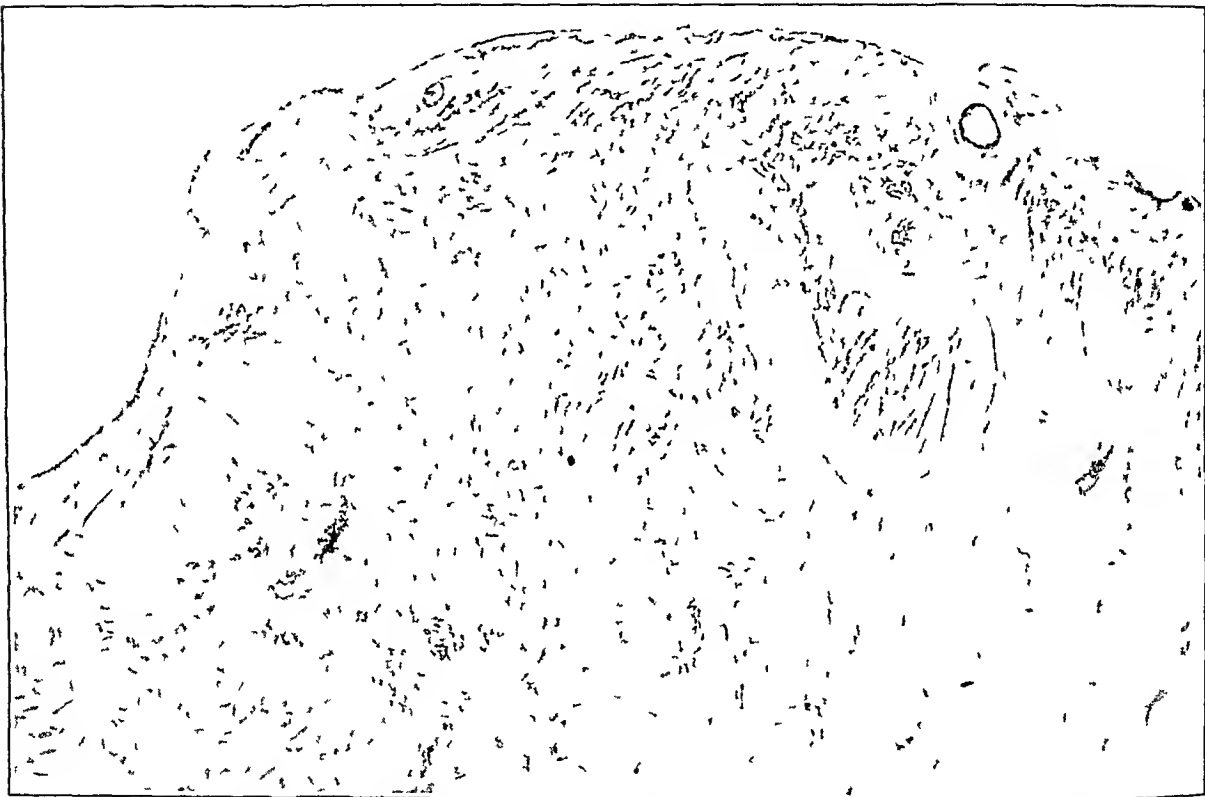


Fig 2 (case 2) —Degenerative nerve tissue removed at operation in a case of syringobulbia, magnification about 57

a lock stitch of silk, and the muscles, fascia and skin were closed with interrupted black silk sutures. The condition of the patient remained excellent throughout the operation, but she received two transfusions of blood, as well as dextrose, during the operation as supportive measures.

*Diagnosis*—The postoperative diagnosis was syringobulbia.

*Postoperative Course*—The patient made an uneventful recovery. On the sixth postoperative day the sutures were removed, and the wound healed by primary intention. The patient was able to get up and about gradually, when she was reexamined on Nov 24, 1943, she was free from headaches but had some subjective dizziness and epigastric distress, with slight nausea and occasional vomiting. She

had slight ataxia in walking but no nystagmus or past pointing. The hyperreflexia remained over the entire right side, and there was slight diminution of sensation over the right side of the forehead and the bridge of the nose, as well as over the left upper extremity. The optic disks and vessels appeared normal. In summary, the symptoms referable to increased intracranial pressure, and to some degree the involvement of the cranial nerves, had regressed satisfactorily at this time. The loss or alteration of function in the long tracts remained about the same. She was discharged from the hospital on Dec 7, 1943.

The patient made a very satisfactory recovery, and after a rest of six months she was able to earn her livelihood as a clerk. When last examined, about eighteen



Fig 3 (case 2)—Tissue similar to that shown in figure 2, magnification about 120

months after operation, she no longer had atrophy of the tongue, and the other signs previously enumerated were minimal. However, she had referred pain about the breast, and the possibility of developing syringomyelia must be entertained.

*Comment on Cases*—"Syringopontobulbia" is the proper designation for the condition in case 1, on the basis of the anatomic location of the lesions and the clinical syndrome. How much part an extension into the midbrain itself may have played in the causation of the pupillary inequality, the slight ptosis of the left lid and the very coarse, alternating tremor of the left arm cannot be determined but is of speculative



interest The differential involvement of the trigeminal nerve is of note, since the pathways for pain and temperature sense, being bulbo-spinal, were barely affected, whereas involvement of the motor nucleus, being pontile, caused complete paralysis The subjective sensation of levitation produced by certain head movements is the most interesting symptom I do not recall that this sensation of being suspended in air has been expressed by any other patient with a cerebellar or cerebello-pontile lesion From the neurophysiologic standpoint, it is difficult to localize, except that it is generically of vestibular pathway origin But whether in this case it was an aberration of transmission of normally engendered stimuli within the semicircular canals or was precipitated by impact of fluid in the syrinx against the intra-axial pathways is, again, a matter for speculation The peculiar tilt of the head, simulating that seen with paralysis of the sternocleidomastoid muscle, was doubtless of vestibular pathway origin The particular type of facial paralysis was somewhat unusual and worthy of note Whereas the lower portions of the face were severely affected, voluntary function in the upper portions was, by contrast, well preserved Yet, as seen on simple observation of the patient's face at rest, the restriction of automatic blinking of the left eye was the signal evidence of a lesion of the lower motor neuron type Inasmuch as the lesion was pontile and the sixth nerve was not affected, I attribute the facial paralysis to involvement of the nucleus, rather than of the pathway or the peripheral course of the nerve The occurrence of syringomyelic states with the Arnold-Chiari syndrome makes the observation that the cerebellar tonsils were herniated into the spinal canal of some importance At operation I accepted this herniation as typical of that observed during operations for tumor of the posterior fossa However, the general symptoms of pressure had occurred late in the illness, and the patient had no papilledema Also, the exploration into the cerebellopontile angle was easily made, as is not the case with tumor Inasmuch as the spinal canal proper was not inspected, it cannot be known whether the elongated tonsils were attached to and drawn down by the spinal cord or whether they were free That the fourth ventricle and the medulla were in their normal position, and not drawn down, is certain These facts are emphasized because of reports in the literature of the association of other fragments of status dysraphicus and myelodysplasia with these syringomyelia-like conditions, as discussed by Lichtenstein<sup>11</sup> and Nelson<sup>12</sup> Such syndromes are the Arnold-Chiari malformation and other syndromes of anomalous

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11 Lichtenstein, B W Distant Neuroanatomic Complications of Spina Bifida (Spinal Dysraphism) Hydrocephalus, Arnold-Chiari Deformity, Stenosis of the Aqueduct of Sylvius, etc , Pathogenesis and Pathology, *Arch Neurol & Psychiat* **47** 195-214 (Feb ) 1942

12 Nelson, J Intramedullary Cavitation Resulting from Adhesive Arachnoiditis, *Arch Neurol & Psychiat* **50** 1-7 (July) 1943

segmental development, usually with defects or abnormalities of the skull and/or spine demonstrable in roentgenograms. In the present cases there were no bony abnormalities. No indications that the cystic degeneration was secondary to an extra-axial cause were noted.

Case 2 represents a syringobulbomyelia and exhibits various features of a lesion in this particular location, simulating the well known syndrome of the posterior inferior cerebellar artery, in the domain of which it occurred. In contrast to the picture in case 1 are the findings referable to the trigeminus in the second case. Whereas in the first case there was complete motor paralysis and little sensory change, in the second case there was of necessity involvement of the descending tract only, and therefore no motor loss, but subjective and objective changes on the forehead and face. Of greater surgical interest, however, is the regression of the atrophy and rigidity of the tongue on the affected side during the postoperative period. This demonstrates that some of the central changes were reversible and that they were due to the hydrostatic pressure primarily, rather than to direct destruction, as one would ordinarily infer.

The observation that the arachnoid membrane was thickened and vascularized over the syrinx requires discussion. It will be noted that adhesive arachnoiditis was the third preoperative diagnosis. Inasmuch as the shocklike sensations occurred over a number of years, on moving the head, and the focal and general increase in pressure developed only within a few months of the time of operation, the arachnoiditis no doubt produced these shocklike sensations, which are typical of such a condition. Furthermore, the cerebellar tonsils were not then displaced into the canal, and their herniation cannot be used to account for these sensations referred downward into the extremities and upward from the neck on flexing the head. Although Nelson<sup>12</sup> and others have mentioned the presence of arachnoidal adhesions in certain cases of status dysraphicus associated with underlying cavitation, in the present case there is no probability that the arachnoidal changes played any part in the production of the cavitation. The cyst was primarily in the medulla, while the adhesions were atlanto-occipital. They were not adhesions of the massive and constricting type which sometimes surround the spinal cord and produce transverse pressure syndromes. This point is worthy of some emphasis because myelopathy and arachnoidal adhesions are not infrequent coincidental occurrences, but the adhesions should not be considered the etiologic factor in the myelopathy unless they are truly bandlike and constrictive.

#### GENERAL COMMENT

The conditions of syringomyelia, syringobulbia and syringopontia are merely topographically different expressions of the same basic

pathologic process. They are due to anomalous congenital dysplasia of ectopic gliogenous cell rests within the neuraxis, and the symptoms are caused by the sequelae of the developmental, maturative and degenerative processes which these undergo. Tamaki and Lubin<sup>13</sup> have demonstrated islands and strands of primitive spongioblasts which proliferate and develop into adult glial tissue. This tissue, with its surrounding abnormal vasculature, undergoes a cycle of degeneration, necrosis and liquefaction as the patient reaches adult life, or often earlier. The cavitation may be single, multilocular or truly syringoid, extending for long distances within the neuraxis. The symptoms are produced in part by direct involvement of nuclear masses or fiber tracts, whose normal location has been supplanted by the hyperplastic cell rests. In part, they arise from disturbance of vascular supply to the normal nerve tissues due to the degeneration and diapedesis and hemorrhage which may occur in the abnormal vessels surrounding the hyperplastic zone. Also in great part, the symptoms are produced by direct pressure on adjacent nerve tissue by the collection of fluid under increased tension within the cavitations. As in the cases cited here and in those reported by other authors in which surgical intervention was beneficial, the relief of this tension resulted in arrest of the progress of the disease, and even recovery of some of the neurologic deficits. In neither of the present cases was any attempt made to obliterate the cavity or to affix a nonabsorbable foreign body to the edges of the myelotomy wound in order to maintain a communication between it and the subarachnoid space. Frazier,<sup>3</sup> in a case with recurrent symptoms, operated a second time and found that the cavity had closed up and refilled with fluid. The second operation benefited the patient materially. In analysis of the cases which he reviewed, Frazier inferred that a technic to keep the cavity open yields the best results. Yet, in examining these results, one finds that in 8 of 16 cases an attempt was made to effect drainage by introducing a foreign body. In 3 cases there was "very little change." In 4 cases "moderate improvement" occurred. In 1 case there was "marked improvement." In 8 other cases drains were not inserted. Of these, "moderate improvement" occurred in 1 and "marked improvement" in 7. Thus, the figures cited by him and the inference drawn do not seem to be in accord, and more of the patients without drains were able to return to work than of the others. Davis<sup>14</sup> cited 10 cases, in which immediate benefit resulted from the operation, although no patient was made free

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13 Tamaki, K., and Lubin, A. J. Pathogenesis of Syringomyelia. Case Illustrating the Process of Cavity Formation from Embryonic Cell Rests, *Arch Neurol & Psychiat* **40** 748-761 (Oct) 1938

14 Davis, L. *The Principles of Neurological Surgery*, ed 2, Philadelphia, Lea & Febiger, 1942

from symptoms. He was equivocal concerning the value of silver clips introduced into the edges of the myelotomy wound in an effort to maintain drainage. The value of introducing a foreign body is doubtful. Not only will nature attempt to close the defect but will also enclose the foreign body with tissue. Furthermore, the production of fluid within the syrinx is not a secretory function. It results from degenerative liquefaction of a mass of abnormal cells which have become inadequately nourished through abnormal blood supply. In my opinion, in most of the cases in which the symptoms demand operation an end stage in the pathologic process will have been reached, and recurrence at the point of operation will not take place.

#### SUMMARY

A case of syringopontia and one of syringobulbia, with direct surgical operation on the pons and the medulla, respectively, are reported, with successful outcome.

In both cases the condition simulated neoplasm clinically, in the relentless progression of symptoms.

In both cases the syndrome of advancing intracranial pressure was relieved.

In the case of syringobulbia the patient recovered from the neurologic deficits and was enabled to earn her own livelihood.

#### CONCLUSIONS

Syringoid myelodysplasias of the brain stem are amenable to surgical intervention.

Operation should be undertaken when the course is relentlessly progressive and the pace of development indicates advancing intracranial compression.

Neurological Institute of New York

# Abstracts from Current Literature

EDITED BY DR BERNARD J ALPERS

## Physiology and Biochemistry

STUDIES OF DISTRIBUTION OF POLIOMYELITIS VIRUS H E PEARSON and R C RENDTORFF, *Am J Hyg* **41** 164, 179 and 188 (March) 1945

Pearson and Rendtorff's first study of the distribution of poliomyelitis virus was concerned with the environment of sporadic cases. Testing stool specimens from almost the entire population of a village where poliomyelitis occurred in an adult, they recovered virus only from the 6 year old son of the patient. Pools of specimens from 127 persons in 39 families were uniformly negative. Of 30 persons associated with a patient with poliomyelitis in a small town, virus was recovered only from the stools of a sibling aged 5 years and from 2 playmates, aged 7 and 5 years, of another family. No virus was detected in the stools of the associates of 2 patients on farms or of 2 patients in a small town. Virus was not recovered from fecal specimens from farm animals or from flies, mosquitoes or the brains and intestines of rats or mice from the environment of these sporadic cases. In the second study stool samples from nearly all the children under 16 years of age were tested for the presence of virus after the occurrence of 2 cases of poliomyelitis in a small town. Members of the families of the patients also were tested. Of 282 persons in 146 families, virus was recovered from the brother and a group of 3 cousins of one of the patients and from children of 8 other families, 5 of these children were 2 years of age. From the degree of association of those found to harbor the virus, it was concluded that personal association was the principal factor involved in the spread of infection within the community. The third study concerned the distribution of virus in a selected district of Fort Worth during the 1943 epidemic of poliomyelitis. Stools from 524 persons were tested for virus by inoculation of monkeys. Six of 8 households representing 27 familial contacts were positive for virus, as were 8 of 45 households containing 80 nonfamilial contacts and 2 of 127 households representing 374 noncontacts. Virus was harbored by adults in 5 of the 6 positive households of familial contacts. Virus was not recovered from specimens of water, sewage, flies, ants, cockroaches or droppings of domestic animals. An agent that produced paralysis in mice and cotton rats was obtained from a pool of brains and intestines from 22 rats from the city dump. No virus was recovered from several batches of mice and rats collected in various other parts of the city.

J A M A

REFRIGERATION ANESTHESIA FOR AMPUTATIONS SERGEI S YUDIN, *Am Rev Soviet Med* **2** 4 (Oct) 1944

Yudin discusses his observations on 106 patients. A total of 120 amputations of the extremities were performed under refrigeration anesthesia. The anesthesia was completely effective in 81 cases and satisfactory in 22 cases. No supplementary anesthesia was needed. In the remaining 3 cases the anesthesia failed. In 1 case the tourniquet became loose, in the second the patient withdrew the leg from the ice, and in the third an attempt was made to refrigerate the leg without a tourniquet. No anesthesia was obtained, and ether was administered.

Data are presented which indicate that refrigeration anesthesia does not diminish the viability of tissues at the amputation stump, nor does it delay healing. The reduced volume of blood circulating through the extremity and the lowered cell metabolism account for the excellent results.

Refrigeration anesthesia possesses definite advantages. It does not introduce an additional toxic agent into the body. The anesthesia is absolutely complete in that it eliminates the conduction of all painful, tactile and other stimuli along the spinal and sympathetic nerve paths. The progressive warming of the stump after the operation gradually restores conductivity in the severed nerves and also provides against excessive stimulation of the receptor centers in the brain, this occurs when the paralyzing influences of local or general anesthesia are removed suddenly. Finally, peripheral vascular collapse is prevented by the retarded absorption of toxins from the stump.

GUTTMAN, Philadelphia

ADAPTATION TO ANOXIA AT DIFFERENT AGE LEVELS. I. A. ARSHAVSKI, *Am Rev Soviet Med* 2 508 (Aug) 1945

Arshavski reports observations on the effect of anoxia on puppies of different ages and on adult dogs. Records were made of the reactions of the cardiovascular and respiratory systems and of the changes in hemoglobin and the erythrocyte count of the blood. In acute experiments, animals of different ages, beginning with those 1 day old, inhaled gas mixtures with varying oxygen concentrations from a bag supplied with a valve. According to the results obtained, the animals may be divided into three age groups: those from 1 to 18 days old, those from 18 to 45 days old and those above 45 days of age, including adults.

The author concludes that the young animal is more susceptible to anoxemia than the adult.

Data obtained on animals were confirmed in experiments on young children. The significant effect of anoxia is disorder of muscular coordination. In adults anoxemia was followed by paralysis of the feet, then of the hands and, finally, of the head musculature. In all children examined, the capacity to support the head in a vertical position was lost as soon as cyanosis appeared. There was recovery within thirty minutes to an hour.

Arshavski concludes that "children and young puppies are much less resistant to moderate oxygen deficiency than are adults. The lower tolerance of the younger organism is due to lack of the adaptive reactions which ensure the resistance of the adult organism to anoxemia."

GUTTMAN, Philadelphia

PERMEABILITY OF THE HEMATO-ENCEPHALIC BARRIER IN MASSIVE ARSENOTHERAPY. E. I. KRICHEVSKAYA and D. I. LASS, *Am Rev Soviet Med* 3 38 (Oct) 1945

Investigations were carried out on 43 patients in an effort to study transfer of arsenic into the cerebrospinal fluid. The subjects included 7 patients with tabes, 3 patients with progressive paralysis, 15 patients with syphilis of the brain, 2 patients with syphilitic meningitis, 1 patient with syphilitic pachymeningitis, 3 patients with syphilitic myelitis, 5 patients with latent syphilis, 5 patients with epidemic chronic encephalitis, 1 patient with epilepsy and 1 patient with Friedreich-Marie disease.

In this study the amounts of arsenic in the blood and the cerebrospinal fluid were determined by the method of Wintersteiner, as modified by Krichevskaya. Ninety-two patients received massive arsenotherapy by the drip method. Arsenic was detected within thirty minutes to five hours after injection of arsphenamine. In none of 49 patients, or 53.3 per cent of those studied, was arsenic found after twenty-four hours. In patients who had inflammatory disease of the meninges, arsenic always penetrated into the cerebrospinal fluid.

The authors state that they established the permeability of the cerebrospinal fluid barrier in more than half the patients with primary and early secondary syphilis without any apparent pathologic changes in the membranes. They state that they "detected arsenic in the cerebrospinal fluid many days and even weeks after the termination of treatment." They present data which indicate that arsenic penetrated into the cerebrospinal fluid in 37 of 49 patients who received massive

arsenotherapy and who had a temperature reaction They assert, "it appears, therefore, that in four-fifths of the patients the temperature was a factor that facilitated the penetration of the barrier"

GUTTMAN, Philadelphia

OXIDATION OF PHOSPHOLIPID CATALYZED BY IRON COMPOUNDS WITH ASCORBIC ACID K A C ELLIOTT and B LIBET, *J Biol Chem* **152** 617, 1944

The respiration of tissue suspensions of brain or liver was stimulated for thirty to forty minutes by the addition of small amounts of iron or an iron-protein complex This stimulation is greatly increased by the addition of ascorbic acid Ascorbic acid alone causes the respiration of hypotonic tissue suspensions to be better maintained but has no effect on isotonic suspensions With purified mixed phospholipid from the brain or liver at a neutral hydrogen ion concentration, ascorbic acid causes some oxygen uptake Ascorbic acid plus iron-protein compound produces rapid initial oxidation, the rate falling off with time The activity of the system varies in a complex manner with varying concentrations of the components Of brain phospholipids, only the cephalin fraction undergoes oxidation with iron and ascorbic acid Linoleic and linolenic acids are oxidized, but more slowly than is mixed phospholipid or cephalin No other reducing agent tried was able to replace ascorbic acid in the system The effects of different iron-protein preparations are not proportional to their iron content Ferritin is less active than ferrin Hemoglobin in small amounts is destroyed by phospholipid and ascorbic acid, giving rise to an active catalyst of the oxidation Cytochrome c and hemin are inactive Cyanide causes little inhibition of, and maintains for a longer time, the effects of iron and ascorbic acid Epinephrine and other phenols are strongly inhibitor Serum is strongly inhibitory, its effect may be largely accounted for by inhibitory effects of calcium and of protein Some amino acids, especially histidine, have pronounced stimulatory and subsequent inhibitory effects on the system

PAGE, Cleveland

STUDIES OF SYNCOPE III DIFFERENTIATION BETWEEN VASODEPRESSOR AND HYSTERICAL FAINTING JOHN ROMANO and GEORGE L ENGEL, *Psychosom Med* **7** 3 (Jan) 1945

Romano and Engel, on the basis of physiologic and psychologic differences, distinguish between fainting related to vegetative neurotic mechanisms and fainting as a hysterical conversion Fainting of the first type, they believe, is a vaso-depressor syncope, in which the emotional experiences are accompanied by changes in the circulatory system which lead to a loss of consciousness This is shown by pallor, sweating, changes in the respiration and pulse and falling blood pressure, so that eventually cerebral anemia and marked distortion of electrical activity of the brain occur In hysterical patients who experience fainting as a conversion symptom there is a notable lack of change in respiration, circulatory dynamics and electrical activity of the brain during the period of unconsciousness

WERMUTH, Philadelphia

THE CLINICAL CHARACTERS OF PAIN W GANADO, *Brit M J* **1** 141 (Feb 3) 1945

Ganado describes pain as a group of distinct feelings, each of which has clinical characteristics of its own The severity of pain depends on the tissues affected and the personality of the person involved Also dependent on the tissues implicated are the power of discrimination, the power of location, the types of reflexes provoked and the quality of pain According to Ganado, at least three types of somatic pain can be distinguished (1) surface pain, from the cutaneous and mucosal surfaces, (2) subsurface, or intermediate, pain, from the subcutaneous tissues (where these are thin), from the submucosae and from some adjacent

structures, when the subcutaneous tissue is very thin, and (3) deep pain, from muscles and from all the sensitive deep tissues in general. These types are discussed somewhat at length

ECHOLS, New Orleans

## Psychiatry and Psychopathology

A PSYCHIATRIC ADVENTURE IN COMPARATIVE PATHOPHYSIOLOGY OF THE INFANT AND ADULT JOSEPH J MICHAELS, *J Nerv & Ment Dis* **100** 49 (July) 1944

Michaels discusses certain broad psychobiologic principles, such as the concepts of repression and regression, of evolution and dissolution of the central nervous system and of the evolutionary process in general, and gives examples of their application in human behavior. In the same way in which certain infantile characteristics, such as enuresis and thumb sucking, may persist into adult life, so may some so-called functional symptoms of a psychosomatic disorder express themselves in a manner which utilizes modes of reacting which are consonant with and characteristic of earlier age periods. Adult visceral somatic dysfunctions may represent a recrudescence of infantile visceral somatic functions. This is well illustrated in anxiety states, in which the rapid respiration and pulse rates and frequency of urination and defecation are conditions which occur in the healthy, physiologic state of infancy. Child's concept of gradients is used to explain the isolated and autonomous action of a function which has become split off to appear as a visceral somatic symptom. Just as certain behavior patterns established in childhood may, under stress, become manifest in adult life, so may infantile physiologic patterns again become dominant over those acquired later, thus reversing the normal sequential series of gradients, in which an earlier life period paces a later one. In infancy anxiety is represented by a generalized startle response, which is the basic reaction to the physiologic and psychologic separation from the mother.

A high degree of homeostatic lability and a variable and inconstant adaptation to both internal and external stimuli are characteristic of infancy, just as a stable and delicately adjustable internal environment is an adult characteristic. Thus, heat regulation, water and mineral balance and the levels of red and white blood cells are all subject to oscillations in infancy, which are not found in normal adult life but which do occur in neurotic persons who are exhibiting autonomic and endocrine infantilism. Similarly, the symptoms and signs of the effort syndrome may be regarded in the sense of a reversion to the infantile condition, in which high and variable respiratory and cardiac rates are usual. The diarrhea, urinary frequency, blushing and cutaneous eruptions of the neurotic adult are other examples of this type of reversion.

The choice of the organ system affected by the psychosomatic disorder may be determined by its fusion with an emotional process at a labile period, when the former had not attained its full maturation.

CHODOFF, Langley Field, Va

WAR AND ITS PSYCHIATRIC PROBLEMS HOWARD P ROME, *J Nerv & Ment Dis* **101** 445 (May) 1945

Rome points out that one effect of war has been to direct psychiatric thinking to the problems of the group rather than to those of the individual. Group and unit action has its principles and rules which cannot be explained by a mere quantitation of the individuals comprising the group. Precise answers are lacking to such questions as the reason for the formation and the nature of groups, what makes a group split, and along what lines, and how can group dissolution be prevented or brought about. Knowledge of these matters is of great importance both in psychologic warfare and in peacetime politics. Examples of the application of group technics in the recent war are the prophylactic value of battle training and inoculation and the success of group psychotherapy.



Returned service men will constitute a problem in group psychiatry. They will probably break up into three predictable segments—a "lost generation" portion, the chronically aggressive group and the comparatively normal and easily readjustable majority.

CHODOFF, Langley Field, Va

SOME NEUROLOGICAL AND NEUROVEGETATIVE PHENOMENA OCCURRING DURING AND AFTER ELECTROSHOCK H H FLEISCHHACKER, *J Nerv & Ment Dis* **102** 185 (Aug) 1945

Fleischhacker reports observations on the physical phenomena occurring during and after electrically produced convulsions in over 70 patients, most of whom were women. The average voltage used was 95 to 120 milliamperes against a resistance of several hundred to 1,000 or more ohms for an average time of 0.2 to 0.4 second.

According to the strength of the stimulus, three levels of petit mal phenomena can be differentiated. These consist of petit mal proper, affective petit mal, characterized by emotional confusion with laughing or crying or moaning, and motor petit mal, characterized by movements, which may be (a) either "coordinate" or "pseudointentional" or (b) "organic," striatal, and then parakinetic, athetoid or jerking in type.

Some of the neurologic phenomena observed during the fit may be influenced by the position in which the electrodes are applied. If one electrode is placed nearer the external acoustic meatus than the other, asymmetric turning or convulsive movements may ensue.

Vegetative and vascular phenomena noted included the occurrence of cutis anserina, sweating and, rarely, dermatographism. The pulse rate rises at the beginning of the fit, may increase or decrease toward the end and usually remains increased for a time after the fit. In some cases a pulse cannot be obtained from the radial or the carotid artery when it is still present in the abdominal aorta.

Through its influence on the diencephalon and, through this, on the pituitary and other endocrine glands, shock treatment has a definite neuroendocrine effect. The appetite is usually stimulated, some patients experience difficulty in sleeping, and there is an irregular effect on menstruation. Ejaculation may occur in some male patients during or immediately after the fit.

No discernible change was noted in samples of cerebrospinal fluid of about 20 patients examined during and after the course of treatment.

CHODOFF, Langley Field, Va

THERAPEUTIC EFFICACY OF ELECTROCONVULSIVE THERAPY GEORGE H ALEXANDER, *J Nerv & Ment Dis* **102** 221 (Sept) 1945

In a previous communication, Alexander pointed out the desirability of utilizing a specific time interval between the termination of shock therapy and the evaluation of results, in order to avoid ascribing the influence of other healing factors to the specific treatment. He proposes that a period of thirty days following the final coma or convulsive treatment should be selected as the upper limit of time during which remissions should be attributed to its specific influence. Classifying treatment as successful only when the patient was able to leave the hospital within thirty days after his last treatment, Alexander reports the results of electroconvulsive therapy in 100 consecutively treated patients and contrasts the results so obtained with those obtained in a group of patients in whom the criterion of successful therapy was the ability of the patient to leave the hospital at some time subsequent to treatment. Using the thirty day criterion, the therapeutic efficacy was 51 per cent for all psychoses, 41 per cent for involutional psychoses, 67 per cent for manic-depressive psychoses, 49 per cent for involutional and manic-depressive psychoses combined and 56 per cent for schizophrenic psychoses. In the group in which the time factor was not considered, the percentages

of successful results were as follows 87 per cent for all psychoses, 84 per cent for involuntional psychoses, 93 per cent for manic-depressive psychoses, 87 per cent for involuntional and manic-depressive psychoses combined and 83 per cent for schizophrenic psychoses

These results lend support to the belief that it is only in cases of mental illness in which recovery with other forms of therapy is possible that electro-convulsive therapy hastens the process

CHODOFF, Langley Field, Va

OUTCOME IN DEMENTIA PRAECOX UNDER ELECTRIC SHOCK THERAPY AS RELATED TO MODE OF ONSET AND TO NUMBER OF CONVULSIONS INDUCED LOUIS LOWINGER and JAMES N HUDDLESON, *J Nerv & Ment Dis* **102** 243 (Sept) 1945

Lowinger and Huddleson report the relation of mode of onset and number of convulsions in 232 young male patients (95 per cent of them veterans of World War II) treated with electric shock There were remissions in 54 per cent after a postshock period averaging three and a half months when the duration of the psychosis had been less than six months before the start of treatment This 54 per cent breaks down into 55 and 50 per cent for cases of acute and insidious onset, respectively The difference according to onset increases with the rise in the preshock duration of the psychosis For a duration of twelve to twenty-three months the remission rates differed greatly, being 21 and 8 per cent for acute and insidious onsets, respectively There were no remissions after a preshock duration of two years or over Regardless of duration, the remission rate for the acute onset was 34 per cent, for the insidious onset it was 15 per cent

For all preshock durations of over six months, courses of sixteen to twenty grand mal treatments yielded no better remission rates than courses of ten to fifteen treatments For a duration of under six months, superior remission rates were obtained with ten to fifteen grand mal treatments The incidence of improvement for all durations was slightly better with sixteen to twenty than with ten to fifteen grand mal treatments Two courses totaling over twenty convulsions were practically useless

CHODOFF, Langley Field, Va

OBJECTIVE PERSONALITY STUDIES IN MIGRAINE BY MEANS OF THE RORSCHACH METHOD W DONALD ROSS and FRANCIS L McNAUGHTON, *Psychosom Med* **7** 73 (March) 1945

Ross and McNaughton made Rorschach records of 50 patients with migraine headaches and compared them with the records of 10 patients with headaches of undoubtedly psychogenic type, 15 patients with headaches of unknown cause, 55 symptom-free persons of superior intelligence, 50 miscellaneous psychoneurotic patients and 24 patients with tumor or injury of the brain The records were analyzed only for objectively defined signs and were interpreted as a group rather than individually The Rorschach method showed that the following personality features were associated with migraine persistence toward success, difficulty in sexual adjustment, perfectionism, conventionality, intolerance and, in general, obsessive-compulsive features

Patients with migraine show some of the characteristics of patients with psychoneuroses and cerebral disease but do not resemble either of these groups in their most characteristic composite Rorschach ratings

WERMUTH, Philadelphia

THE RORSCHACH PERFORMANCE WITH NEUROCIRCULATORY ASTHENIA W D ROSS, *Psychosom Med* **7** 80 (March) 1945

Ross studied 50 persons with neurocirculatory asthenia by the quantitative Rorschach method and compared the results with those for several control groups The personality features of the patients with neurocirculatory asthenia included a tendency to give up easily under stress and an obsessional conscientiousness,

which made their problems appear unduly difficult to them. The patients with longer-standing conditions possessed neurotic features to a greater degree, while the patients whose disturbance was of recent onset showed more obsessional characteristics and in this respect resembled in personality the patients with migraine, as reported in a similar study

WERMUTH, Philadelphia

ELECTRONARCOSIS CLINICAL COMPARISON WITH ELECTROSHOCK GEORGE N THOMPSON, JAMES E MCGINNIS, A VAN HARREVELD, C A G WIERSMA and ESTHER BOGEN TIETZ, War Med 6 158 (Sept) 1944

In the standardized electronarcosis technic an electronic instrument is used. This delivers a 60 cycle alternating current, which automatically compensates for moderate changes in resistance of the patient's circuit. A current of 160 to 250 milliamperes is applied through electrodes placed bitemporally (in terms of cerebral topography, bifrontally). The current is maintained at the initial level for thirty seconds, during which the patient has a tonic spasm, at the end of thirty seconds the current is decreased to 60 or 75 milliamperes, and at this time the patient usually shows a few mild clonic contractions. After sixty to seventy-five seconds the current is raised gradually at the rate of 5 milliamperes every fifteen seconds, to a maximum of 125 milliamperes at the end of five minutes. For reasons of standardization the treatment is usually terminated at the end of seven minutes.

The authors compared the cardiovascular responses, respiration, autonomic responses, ocular reflexes, tonic reflexes, pathologic reflexes and certain other abnormal neurologic signs in 50 patients seen during electronarcosis with those in 50 patients treated with electroshock and with those in 4 patients treated with a 200 milliamperes current for thirty seconds.

In all three groups there was an initial cardiac arrest, lasting from three to seven seconds. Tachycardia began in electroshock after twenty seconds and returned to normal in a few minutes. In long-continued electroshock and in electronarcosis it began after thirty seconds and lasted throughout the shock, continuing at times for fifteen to twenty minutes.

In standard electroshock and in long-continued electroshock the blood pressure rose and returned to normal in three seconds. In electronarcosis the blood pressure returned to a level of 140 to 160 systolic and 90 to 110 diastolic during the first sixty seconds. It then began to climb, reaching levels of 170 to 220 systolic and 100 to 120 diastolic, where it remained until the current was cut.

In electronarcosis deep respirations continued for the duration of the treatment and maintained their depth and rhythmicity. In electroshock the respirations became more and more shallow during the first five to seven minutes after the current was stopped. In electronarcosis respiratory stridor occurred as the current was increased.

With all types of treatment autonomic flushing of the skin and pilomotor reactions occurred, but pilomotor contractions existed throughout the electronarcosis treatment. Sweating was more common with electronarcosis. In electroshock pupillary reflex to light was present, but in electronarcosis the pupils became miotic and remained fixed to light throughout the treatment.

In electronarcosis prolonged flexor tone and forced grasping were observed. These occur during deep insulin coma but are not present in electroshock.

The authors conclude that although electronarcosis has been used as an anesthetic agent for animals in its present status it is not practical as an anesthetic device for human beings.

PEARSON, Philadelphia

WAR NEUROSES PSYCHIATRIC EXPERIENCES AND MANAGEMENT ON A PACIFIC ISLAND MEYER A ZELIGS, War Med 6 166 (Sept) 1944

In the new type of interisland warfare that was waged in the Pacific, fatigue, disturbed sleep, exposure to repeated noise or blast concussion and harassment

by the enemy are the common factors which contribute to the ultimate breakdown of previously stable persons when they are placed in a combat area. When to these are added the factors of geographic isolation, confinement to a small area, humid climate, lack of recreational facilities, no opportunity for leave and inability to retaliate or to unleash emotionally aggressive drives, there will be an increasing number of cases of neurosis.

Because of the locale and the particular factors involved, indications for evacuation of patients suffering from neurosis will differ from those which obtain in large scale land operations. Periods of duty in such theaters must necessarily be lessened, and rotation of personnel to different stations within the same area should be made possible if the incidence of operational fatigue and war neurosis is to be kept low. Effective psychotherapy of patients in the field is at best a difficult, and often a futile, procedure. The disheartening fact that less than 10 per cent of patients in this group improved when retained in the combat area forms the basis for this belief. From this limited experience it follows that prompt evacuation to a secure area constitutes one of the first essential steps in the treatment of such casualties. What the further disposition should be will depend to a great extent on the age, symptoms and response to early treatment. In general, persons who are older, married and with children will benefit more by return to their families, while the younger, more dependent, ones may be better rehabilitated away from home.

PEARSON, Philadelphia

A PSYCHOMETRIC STUDY OF SENILITY H. HALSTEAD, *J. Ment. Sc.* 89 363 (July-Oct) 1943

Halstead describes a tentative battery of twenty-five short tests for the measurement of senescence. The functions tested included the "primary mental abilities"—verbal comprehension, word fluency, space, number factor, memorizing and induction or reasoning. The scale was the result of the application of nearly eighty tests to senile patients. The tests were classified into three groups according to the degree of difficulty experienced by the senile subjects. The most difficult tests were those in which the subjects were required to break away from old mental habits and to adapt to unfamiliar situations—tests of recent memory (logical), of judgment, planning and reasoning, and tests embodying difficult or lengthy instructions. Less difficulty was found with such tests as rote memory, fluency of associations, simple arithmetic and vocabulary. Performance was least affected on tests of visual recognition, old mental habits and simple motor tasks.

The tests for senility should be short because of straying attention, impaired comprehension and short retention. Perseveration is greatly increased in senescence. There was loss of steadiness and speed on the motor side.

The present mental status of the patients was estimated on the basis of eleven tests scored on the mental age method, the average mental age was between 10 and 11. An estimate of the former mental status of each patient was made by means of efficiency quotients on part of the Bellevue scale. A table comparing the present and the former mental status is shown.

KATZ, Boston,

PSYCHOSOMATIC CASUALTIES IN THE MIDDLE EAST ALFRED TORRIE, *Lancet* 1 139 (Jan. 29) 1944

Torrie discusses 2,500 patients treated in a psychiatric base hospital in North Africa during the retreat from El Alamein and the advance from there to Tripolitania. He says he uses "the term psychosomatic deliberately in place of psychiatric and in a wider sense than is usual to emphasize body-mind unity." The diagnoses, in their order of frequency, were anxiety neurosis, hysteria, psychopathic personality, endogenous depression, mental dulness, schizophrenia, organic states, paranoid states, reactive depression, neurasthenia, physical exhaustion, mania and obsessive-compulsive neurosis. The organic states were those the mental symptoms of which were secondary to or caused by a physical disability.

A higher proportion of casualties was found in "units with little cooperative life, such as small teams of drivers in the lines of communication" Married men showed a higher rate than single men The author believes that irregular mail from home helps to make matters worse The outstanding precipitating factor was an explosive battle episode Change from a unit with good morale to one with lack of faith in the leader was an important factor also

Of the first 1,201 patients discharged from the neurosis division, 51.6 per cent returned to full duty and 35.5 per cent to duty outside the battle area Of these, 1,000 had anxiety neuroses and hysteria Only 6 men had obsessional neuroses The neuroses last mentioned, Torrie says, "are rarer than in civil practice because there is lessened guilt over unconscious aggressive impulses, these being sanctioned and indeed encouraged during wartime" Among these 1,000 patients headache was the prevalent symptom It may have been physiologic at first, but later it became the main preoccupation Anxiety, ranging from apprehension and fear to terror and panic, and tremors or tremulousness were next most common It was often wise to have patients complaining of sleeplessness awakened now and again to show them that they slept well

Of the 1,000 men with anxiety neuroses and hysteria, few had actual conversion hysteria, and 92 were subjected to rapid psychoanalysis The main etiologic factor elicited was separation anxiety In most cases a prototype for the adult reaction was found in the childhood history

A ward environment was aimed at in which the soldier was surrounded by influences formerly lacking in his family situation, so that he could work out with the physician his conflict over aggression "In treatment the purpose was to remove symptoms and bring the soldier back to his condition before illness and to remove, if possible, the underlying cause" Hypnosis, ordinary or chemical, helped to remove symptoms but was not so valuable in securing insight for the patient as for the physician Prolonged narcosis, chiefly induced with diethyl-diallylbarbiturate of diethylamine (sominifaine), was given to the patients with the severer illnesses, who were too acutely ill for other than physical approach Of the 174 such patients, 30 to 40 per cent returned to full duty Insulin and analeptic drugs and electric shock were used with good effect in some cases, and when indicated placebos were used in other cases

The patients were discussed with the sister each morning, and her part as the "good mother" in charge of the ward was felt to be very important Patients who did not show a recovery trend, and patients with conversion hysteria were felt to have a bad influence on other patients The author believes a definite date of discharge should be given if possible, for it accelerates recovery in most patients, although it makes a few worse and thus indicates need for further treatment

Psychotherapeutic interviews were given groups of 12 men at intervals Hypothetic situations similar to their own personal difficulties were used, and afterward comments were encouraged from all Group spirit was found to be poor at first After the discussion each patient went to his daily job in the camp which he had chosen from a group of some twenty occupations It was found that in occupational therapy the man in charge was more important than the materials used

No illusions were held as to the chances of recurrence in the men Patients treated with psychotherapy stayed on an average of eighteen and one-tenth days

The author believes that civilian hospitals might benefit by making sure that neurotic patients up and about are actively employed

McCARTER, Philadelphia

ACCIDENTS IN SHOCK THERAPY CELSO PEREIRA DA SILVA and PAULO FERREIRA DE BARROS, Arq assist psicopat estad São Paulo 9 107 (March-June) 1944

The authors report the occurrence of 16 accidents involving the bones and joints among 1,843 patients given shock therapy, 1,500 received metrazol shock

and 343 electric shock therapy Three patients sustained fractures of the neck of both femurs, 2, unilateral fracture of the femur, 1, a fracture of the horizontal ramus of the os pubis, and 1, a fracture of the neck of the humerus, 1 had a comminuted fracture of the neck of the humerus with dislocation of the shoulder on the same side, 1 each, fracture of the clavicle, scapula and acromion process, 4, fractures of three or four dorsal vertebrae, and 1, a dislocation of the shoulder Of these 16 patients with complicating accidents, 4 had hebephrenic schizophrenia, 1 the hebephrenocatatonic type and 1 the hebephrenoparanoid type, 1 had paranoid, 1 catatonic and 2 unclassified forms of schizophrenia, 2 had paraphrenia, 1 mental deficiency with a psychotic episode, and 1, hysteroepilepsy In 5 patients the injury occurred during the first treatment, in 5 others, during the second treatment, in 1, during the third treatment, in 2, during the fourth treatment, and in 2, during the fifth treatment There were 13 complications among 1,500 patients treated with metrazol (0.86 per cent), and 3, among 343 patients treated with electric shock therapy (0.87 per cent) The youngest of the 16 patients was 21 years of age and the oldest 55, most of the patients were between 32 and 39 years old Age did not seem to be a factor in the complications The authors found no roentgenologic evidence of disease of the bone or of defective bone structure to indicate a predisposition to the complications The duration of the illness of the patients treated also was not considered a significant factor The authors believe that the type of restraint during treatment may have played a role They do not, however, present any convincing statistics Except for the bilateral fractures of the femurs, the prognoses for the skeletal complications were good

SAVITSKY, New York

### Meninges and Blood Vessels

CEREBELLAR, DYSKINETIC AND ALTERNATING SENSORY SYNDROMES CAUSED BY ANEURYSM IN THE REGION OF THE PONS VICENTE DIMITRI and JULIO ARANOVICH, *Rev neurol de Buenos Aires* 9 295 (Oct-Dec) 1944

The authors report the third case of aneurysm of the superior cerebellar artery to be recorded Bristowe reported a case in 1858 and MacSwiney a case in 1875

A 30 year old farm laborer was admitted to the hospital five years after receiving a bullet wound, a bullet entered the region of the right ear and emerged from the left preauricular region A few months later a sympathectomy was done for relief of exophthalmos on the right side Diplopia and external strabismus of the right eye persisted Four years after the injury the patient began to complain of dizziness and paresthesias on the left side of the body, with increasing difficulty in walking Examination one year after admission showed bilateral exophthalmos, more prominent on the right side, paralysis of the right external rectus muscle, nystagmus, anisocoria, with sluggish reactions to light on both sides, and atrophy of both optic nerves with retinal hemorrhages There was marked diminution of visual acuity, which rapidly progressed to blindness Weakness of the lower left side of the face and nasal dysarthria were also noted

The patient exhibited choreiform movements of both sides of the body while sitting Tremors of the head and then of other parts of the body appeared especially with any kind of effort, such as talking or moving the head forward The movements usually began in the head, extending to the rest of the body and ending in a series of violent contractions of the entire body They were usually followed by a variable period of relative freedom from tremors The slightest movement brought on similar dyskinetic phenomena The patient was able to lie quietly on his back with the upper limbs semiflexed, his hands on his abdomen and the lower limbs in extension On his attempting to change his position, the abnormal movements just described appeared Pronounced dystonia was noted in all four limbs with passive movements, hypotonia alternating with fleeting increase in tonus Passive movements of the joints and of the head also resulted

in coarse tremor. There were weakness and exaggeration of the tendon reflexes on the left side, and the abdominal and cremasteric reflexes were diminished, with a bilateral Babinski sign. There were bilateral marked cerebellar signs (dysmetria, heel to knee and finger to nose ataxia and adiadosokinesia), an alternating sensory syndrome on the right side of the face and left side of the body with a syringomyelic type of dissociation, left astereognosis and complete blindness due to secondary optic atrophy. The spinal fluid pressure was 70 (Claude), the albumin 40 mg, with 4 lymphocytes in the fluid. The patient died seven years after the onset of illness.

A large tumor was observed lying at the base of the brain, compressing the right side of the brain stem and extending rostrally from the level of the pontobulbar junction caudally to the bulbocerebellar angle. In its widest part it measured 5.3 cm, the maximum anteroposterior dimension was 3.4 cm. The tumor was connected with the right superior cerebellar artery. There was displacement of the brain stem to the left, with extensive destruction of the right side of the base of the pons. Microscopic examination showed that the tumor was an aneurysm. Fragmentation of the media of the aneurysm with accumulation of iron pigment was considered evidence of trauma. Softenings were observed in the white matter of the right temporal lobe and in the right quadrilateral lobe. There was destruction of the greater part of the right middle peduncle, the homolateral restiform body, the right descending root of the fifth cranial nerve and the right spinocerebellar pathways and atrophy of the olives. The red nucleus was intact. The function of the medial fillet was apparently impaired by compression. There was also evidence of increased intracranial pressure, as seen in flattening of the convolutions and dilatation of the ventricles, probably due to closure of the aqueduct.

The unusual dyskinetic syndrome was considered a result of involvement of afferent and inhibition of efferent cerebellar pathways.

SAVITSKY, New York

## Diseases of the Brain

MIGRAINE HEADACHE. SOME CLINICAL OBSERVATIONS ON THE VASCULAR MECHANISM AND ITS CONTROL. MILES ATKINSON, *Ann Int Med* **21** 990 (Dec) 1944

Atkinson reports his observations on 21 patients with uncomplicated migraine who were followed over periods varying from six months to two years. Each patient was subjected to an intradermal test with histamine. Negative results were reported for each patient. According to Atkinson, these observations indicate that "no case owned a primary vasodilator mechanism, that every one of the 21 cases of typical uncomplicated migraine owned a primary vasoconstrictor mechanism."

Atkinson administers nicotinic acid, for its vasodilator action, to migrainous patients. The regimen is as follows. From 25 to 30 mg is injected intramuscularly in order to determine, by the extent of the flush reaction, the individual tolerance of the patient. From this reaction subsequent doses may be estimated, and a series of six to eight intravenous injections is given, starting with 20 to 30 mg and increasing by daily increments of 5 mg up to 50 mg or such lower limits of tolerance as may be determined. A dose higher than 50 mg is seldom required. After the course of intravenous injections the patient is taught to give himself intramuscular injections of such doses (25 to 50 mg) and at such intervals (daily or three per week) as experience and the severity of the symptoms indicate. At the same time the drug is given in tablet form (50 to 150 mg daily). After a period, which is determined by the clinical response to treatment, the patient is weaned from the injections and kept on a maintenance dose given by mouth. A high protein-low carbohydrate diet is recommended and advice given as to rest and

exercise and the beneficial effects on the vasomotor system of alternating warm and cool showers. Smoking is discountenanced and, when possible, stopped, on the grounds that migraine is a peripheral vascular disorder.

The results of this treatment were as follows: complete relief in 2 patients (followed over periods of four and six months), great improvement in 10 patients and moderate improvement in 5 patients. The treatment failed to relieve 4 patients.

Atkinson discusses the mechanism of the migraine syndrome. Migraine may be due to more than one cause. "It may be the result of such diverse conditions as vasospasm, allergy, exudative diathesis or endocrine disturbance."

The rationale for the use of nicotinic acid is the production of vasodilatation and thus an attack on the primary vasoconstriction which occurs prior to the onset of the headache.

GUTTMAN, Philadelphia

ELECTROENCEPHALOGRAPHIC FINDINGS DURING AND AFTER ACUTE ENCEPHALITIS AND MENINGOENCEPHALITIS. IRA S. ROSS, J. NEIV & MENT. DIS. **102** 172 (Aug) 1945

Ross investigated the electroencephalographic activity in 4 children during and after the acute stages of encephalitis. Gross disturbances were found in each patient. The abnormalities were generalized and consisted of slow, bilaterally synchronous waves of enlarged amplitude. The records were nonspecific, and the degree of the electroencephalographic disturbances was sometimes out of proportion to the mildness of the clinical symptoms. The disturbances in electrical activity of the brain may outlast the acute phase of the inflammatory process and in some cases may simulate the dysrhythmia associated with convulsive disorder, as well as the changes found in patients suffering from tumor of the brain.

CHODOFF, Langley Field, Va

THE SYNDROME OF THE POSTERIOR INFERIOR CEREBELLAR ARTERY RESULTING FROM A METASTATIC NEOPLASM. CHARLES DAVISON and LEO A. SPIEGEL, J. Neuro-path & Exper. Neurol. **4** 172 (April) 1945

Davison and Spiegel report their observations on 2 patients who presented neurologic evidence of the syndrome of the posterior inferior cerebellar artery. Both patients had primary carcinoma of the lung.

In the first case, the mental changes, which consisted of mood swings from naïveté and coyness to anger and aphasia, and signs referable to the pyramidal tract, which were more evident on the right side, were undoubtedly caused by a neoplasm in the left cerebral hemisphere. The Horner syndrome of the right, the sensory disturbances of the right side of the face and the contralateral sensory disturbances of the body, together with paralysis of the right side of the palate and uvula, were the result of a tumor which had metastasized to the lateral side of the medulla oblongata along the distribution of the posterior inferior cerebellar artery. In this case cerebellar signs could not be detected. Their absence remains unexplained, unless the signs of involvement of the pyramidal tract on that side interfered with the proper elicitation of indications of cerebellar involvement. There are occasional instances of occlusion of the posterior inferior cerebellar artery without cerebellar signs. In the present case the restiforme body was only slightly involved. The bilateral signs of damage to the pyramidal tract were readily explained by the lesion in the left cerebral hemisphere and that in the right cerebral peduncle. The sensory disturbances over the body below the ninth thoracic segment were best explained by the probability that not all the spinothalamic fibers were destroyed. The tumor cells in this case, and possibly in the second case as well, migrated from the lung by the blood stream and reached the posterior inferior cerebellar artery by way of the right vertebral artery, of which the former is a branch. The posterior inferior cerebellar artery may also take its origin from the basilar artery.



In the second case the clinical syndrome of the posterior inferior cerebellar artery was clearcut. The patient had cerebellar signs, which were lacking in the first case. It is believed that the dorsolateral part of the right side of the medulla oblongata was involved in this instance. No necropsy observations were available.

GUTTMAN, Philadelphia

MILITARY ASPECTS OF NARCOLEPSY MAX LEVIN, War Med 6 162 (Sept) 1944

Twenty-five soldiers discovered asleep on post as sentinel were found to fall into three groups: 4 rebellious psychopathic men, who fell asleep intentionally, 19 good soldiers, who fell asleep because they more or less "carelessly" had failed to get enough sleep before going on post, and 2 men suffering from narcolepsy.

The military significance of narcolepsy is not limited to the fact that it is responsible for an occasional sentinel's falling asleep. There are other situations facing the soldier which appear to favor morbid sleep. These situations are comparable to the conditions which give rise to "inhibition" in the Pavlov experiments, and the tendency of men with narcolepsy (manifest or latent) to fall asleep in these situations supports the hypothesis that narcolepsy arises from undue "inhibitability" (susceptibility to inhibition) of cerebral cells.

PEARSON, Philadelphia

INTRACRANIAL ANEURYSM OF THE INTERNAL CAROTID ARTERY JOSE M. MAINETTI and HUGO R. ORLANDI, Rev med d Hosp ital de La Plata 1 19 (Oct-Dec) 1944

Mainetti and Orlandi report the case of a woman aged 65 whose illness had begun a year prior to her admission with headaches, diplopia on right lateral gaze and dizziness. She continued to have recurrent severe pain around the right eye. Twenty-five days prior to admission to the hospital she was awakened by severe pain around the right eye, followed by headache and vomiting. Complete drooping of the right lid occurred at the same time. On admission, she also had dizziness, vomiting, a tendency to fall to either side while walking, hyperacusis and some difficulty with chewing. On examination, there were diminution of pain, touch and temperature sensations in the first division of the right fifth nerve, anesthesia of the right cornea, complete ptosis of the right eyelid and external and internal ophthalmoplegia on the right side. There were also definite involvement of the motor portion of the right cranial nerve, diminution of smell on the right side, diminution of pain in the anterior third of the right side of the tongue and labyrinthine hyperexcitability. The blood pressure was 190 systolic and 100 diastolic. The Wassermann reaction of the blood was negative. Examination of the spinal fluid showed a normal condition. An air encephalogram showed a mass pushing up the temporal horn of the lateral ventricle on the right and some displacement of the third ventricle. The preoperative diagnosis was neoplasm of the posterior fossa, probably in one of the cerebellopontine angles. No tumor was observed at operation. At autopsy an aneurysm of the intracranial portion of the right internal carotid artery was disclosed. Histologic studies of the aneurysm showed it to be of arteriosclerotic origin. There was no intracarotid injection of a contrast medium.

SAVITSKY, New York

RELATION OF TRAUMA TO JUVENILE DEMENTIA PARALYTICA CLINICOPATHOLOGIC AND MEDICOLEGAL STUDY JOSÉ PEREYRA KAER, Rev neurol de Buenos Aires 9 117 (April-June) 1944

Pereyra Kaer reports the case of a 12 year old boy, who was admitted to the hospital on May 18, 1937 and died Oct 20, 1937. The father was alcoholic. There was no history of venereal disease. The patient began to talk at 1 year and to walk at 18 months of age. There was a definite history of retardation in school, his behavior was otherwise normal. The boy was able to shop in the neighborhood and to play, although he was nervous and at times difficult to manage. On June 6,

1935, when 10 years old, he was struck by a truck while crossing the street. There was a short period of unconsciousness, he sustained a small contusion in the left frontal region, an abrasion over the nose, a fracture in the middle third of the right tibia and a hematoma of the left eyelid. In four months he was entirely well and had no complaints.

In February 1937, about twenty months after the accident, he showed increased irritability, with progressively defective attention, pronounced alterations in conduct, disobedience, aggressiveness and impairment of speech. There was also gradual weakness of the left extremities. Two months later, in April 1937, he became incontinent. The pupils were unequal and fixed to light, there was weakness of the left side of the face, and spastic hemiplegia and hyperreflexia on the left side. The course was progressively downhill, and the patient died on October 20. The spinal fluid contained 18 lymphocytes per cubic millimeter and gave a 3 plus Pandy and a 3 plus Wassermann reaction. The Wassermann reaction of the blood was positive. Autopsy revealed the typical changes of dementia paralytica, with multiple scars in the convexity of the occipital lobes and in the base of the left frontal lobe, unquestionably of traumatic nature.

Although bridging symptoms were absent and the concussion was not very severe, the presence of the multiple traumatic scars makes it impossible to ignore the probable etiologic role of the head trauma, sustained two years before the onset of the dementia paralytica. Such traumatic scars can be present without clinical signs or symptoms. They create a *locus minoris resistentiae* in the brain.

SAVITSKY, New York

STURGE-WEBER-DIMITRI DISEASE [NEVOID AMFNTIA] J. BEBIN, *Rev de neuro-psiquiat* 7 432, 1944

Bebin states that Dimitri described the disease in 1923 independently of Weber, who recorded his case in 1922. Nussey and Miller collected 139 cases of the disease in 1939. The clinical picture of Sturge-Weber-Dimitri disease consists in facial nevi, glaucoma and signs of cerebral disease. Roentgenologic evidence of intracerebral calcification is usually present. Calcification may be within the brain substance or in the walls of the vessels, which are enlarged and thickened. The changes are most pronounced in the occipital lobes. The author reports 5 cases, without pathologic studies. In 1 case the nevus involved the distribution of the entire left trigeminal nerve, in another, only the distribution of the third division, and in 2 others, the area of the upper two divisions. In 1 case there was a small angioma near the angle of the mouth. All 5 patients had epilepsy and 2 gave a history of attacks of migraine. One had distal hemiatrophy of the left extremities, with hyperreflexia and a Babinski sign on that side. Two of the 5 patients had glaucoma. Only 1 patient showed intracranial calcification. None of the patients was treated surgically.

SAVITSKY, New York

EPITHELIOMA OF THE CHOROID PLEXUS OF THE FOURTH VENTRICLE JULIO ESPINOZA, RUBEN PERINO and H. VILCHES, *Rev de psiquiat y disc conexas* 9 100, 1944

The authors report a verified case of epithelioma of the choroid plexus of the fourth ventricle in a 12 year old boy. The child was admitted with a history of persistently severe headaches for seven months. Vomiting with accompanying exacerbations of headache, dizziness, bilateral tinnitus and diminution of vision had been present for a month. Examination showed diminished vision, bilateral papilledema, weakness of the right side of the face of mimetic type, cerebellar gait with dysmetria, impaired response to the Barany test on the right side and counterclockwise nystagmus. Roentgenograms of the skull showed separation of sutures, erosion of the anterior clinoid processes and displacement and calcification of the pineal gland. Ventriculographic examination showed symmetrically dilated

lateral ventricles and dilatation of the aqueduct of Sylvius and of the fourth ventricle, which was pushed upward

An epithelioma arising from the choroid plexus of the fourth ventricle was successfully removed. The patient did well except for transitory diminution of hearing and persistence of cerebellar signs two months after the operation. Vision improved.

SAVITSKY, New York

CORTICAL DEAFNESS J LEMOYNE, *Ann d'oto-laryng* 10 133 (Oct-Dec) 1944

Lemoine says that the auditory tract is only partially crossed and that a unilateral temporal lesion does not impair hearing. The auditory tract has two relays and comprises three neurons. The first neuron runs from Corti's ganglion to the bulbar nuclei, this is the cochlear nerve. The second neuron, or the bulbo-diencephalic neuron, runs from the dorsal and ventral bulbar nuclei to the internal geniculate body. In this second segment the auditory tract is partly crossed. The crossed bundle comprises a superficial part (acoustic striae of the fourth ventricle) and a deep part, which at the level of the corpus trapezoideum constitutes the chief intercrossing of the auditory tract. The third neuron, the auditory radiations, runs from the internal geniculate body to the transverse temporal convolution, which comprises the center of the cortical projection of the auditory tract. This segment of the auditory tract assumes a special importance in the study of cortical deafness. The author presents the history of a patient with two associated types of disturbances: (1) severe bilateral hypacusia with dissociation of air and bone perception, (2) psychic deafness with total agnosia and disturbances of Wernicke's aphasia. He discusses the existence of cortical deafness and the differentiation of cortical deafness and bilateral labyrinthine deafness. The requirement of lesions involving the two transverse temporal convolutions explains the rarity of cortical deafness. A right temporal lesion has no effect, a left temporal lesion either has no effect or causes Wernicke's aphasia, in cases of bilateral temporal lesions either aphasia is evident or cortical deafness can pass unobserved and requires systematic investigations with the audiometer, or cortical deafness dominates but gives the impression of a labyrinthine deafness.

J A M A

### Diseases of the Spinal Cord

POLIOMYELITIS AND RECENT TONSILLECTOMY J A ANDERSON, *J Pediat* 27 68 (July) 1945

In 1943 Utah experienced the most severe epidemic of poliomyelitis in its history and had more cases per capita of population than any other state. Because of limited facilities for treatment of contagious diseases, only those patients were hospitalized who were reported by the local physician to have bulbar or respiratory involvement, to the exclusion of the patients with spinal involvement. This resulted in the admission of practically all the patients with clinically recognizable bulbar and respiratory forms. Of a total of 400 patients, 136 were hospitalized. The frequency with which a history of recent tonsillectomy was encountered in cases of the bulbar or bulbospinal type was the reason that a questionnaire was sent to 334 physicians in the state requesting the following information: (1) the number of tonsillectomies on children between 3 and 16 years of age done by them in July, August and September 1943, (2) the number of cases of poliomyelitis following recent tonsillectomy in these three months, (3) the age, sex and name of the child, (4) the interval between operation and the onset of symptoms, (5) the doctor's name, if he wished, or (6) the county in which he practiced. It was observed that 43 per cent of the cases of the bulbar and bulbospinal type were preceded by a tonsillectomy within thirty days of the onset. The incidence of poliomyelitis in recently tonsillectomized children was found to be 26 times as great as that in the general child population. The incidence of the bulbar and bulbospinal type of poliomyelitis was found to be sixteen times as great in recently tonsillectomized children as in the general child population.

J A M A

DERMATOLOGIC ASPECTS OF POLIOMYELITIS J G REYES, New York State J Med  
45 1673 (Aug 1) 1945

During the recent poliomyelitis epidemic in New York city, Reyes observed 84 children, their ages varying from infancy to 14 years, admitted to St Francis Hospital with the diagnosis of poliomyelitis. The disease was more common in boys than in girls, the ratio being 5 to 1. In 98 per cent of the children lesions were located on both infrapatellar areas, on the anterior and lateral aspects of both ankle joints, on the dorsa of both feet, on both soles and on the malleoli. The lesions were symmetric and were typically those of hyperkeratinization in the form of plaques, small papules or slightly verrucous elevations, with roughness and dryness of the skin of the legs. Lesions of these types and forms are encountered in cases of vitamin A deficiency. Their abundance seemed to be proportional to the severity of the poliomyelitic involvement, their prominence disappearing with the abatement of the disease. Among the children who were admitted for other lesions, only 1 in 8 had such cutaneous manifestations. From the extremely high incidence of these lesions of the skin in cases of poliomyelitis, Reyes deduces that vitamin A deficiency may be a predisposing factor of poliomyelitis. He advises that a diet rich in vitamin A should be given to all children, especially during the periods of epidemics, and this diet should be supplemented with cod liver oil or its concentrates. Since vitamin A deficiency will produce keratinization of the epithelium of the skin and the mucous membranes of the internal systems, it is possible that these structures which have been affected by the keratinizing metaplasia are open doors for the entrance of the poliomyelitis virus into the human body. It should be investigated whether the administration of vitamin A, either by mouth or parenterally, is of value in the treatment of poliomyelitis.

J A M A

SYNDROME OF AMYOTROPHIC LATERAL SCLEROSIS CAUSED BY CERVICAL "HOURLASS TUMOR" T DE LEHOCZKY and L PIRI, *Confinia neurol* 6 71, 1944

De Lehoczky and Piri report the case of a neurogenous, epidural and paravertebral tumor in a boy aged 16 years. Two years prior to admission the boy had experienced pain in the neck and, later, pain in the left hand, with increasing weakness and paresthesia in the left arm and in the right leg. On admission, neither pain nor paresthesia was present, but the patient's strength was diminished and his muscles were atrophic. There was an egg-sized tumor in the left supraclavicular fossa, which could be traced to the left transverse process of the sixth and seventh cervical vertebrae. The sixth cervical intravertebral foramen was enlarged on the left side. The tumor, 9.5 cm in length and 3.7 cm in width, was removed in one piece through cervical approach without resort to laminectomy. On microscopic examination the tumor proved to be a typical neurilemmoma. It is suggested that the hourglass tumor gave rise to the symptoms by pressure of its intraspinal prolongation on the ventral part of the cord, the anterior pyramidal tract and the anterior gray horn cells. The removal of the tumor was followed by rapid improvement in the severe paralytic syndrome. This may be explained because of the epidural location of the intraspinal part of the tumor.

J A M A

HEINE-MEDIN DISEASE IN THE ADULT CARLOS FONSO GANDOLFO, HUMBERTO R. RUGIERO, CARLOS CRIVELLARI and LEON CHAROSKY, *Prensa med argent.*  
31-1569 (Aug 16) 1944

Other investigators of poliomyelitis have emphasized the rarity of its occurrence in adults. The authors report 48 of 150 cases in patients over 14 years of age. Racial status, profession, sex and family history seemed to play no role in account-

ing for the appearance of the disease. The clinical picture differed in no way from that encountered in young patients, the spinal fluid findings were also the same. The authors did not note polynucleosis in the early stages of the disease, as reported by others.

SAVITSKY, New York

SPONTANEOUS SUBARACHNOID HEMORRHAGE WITH PARAPLEGIA FOLLOWING INTRATHECAL TREATMENT WITH SULFAPYRIDINE. JUAN J. LAZARTE, *Rev de neuro-psiquiat* 7:355, 1944

A half-breed chauffeur, aged 25, suddenly became dizzy and experienced severe pain in the back of the neck. He was able to drive his car home, though his vision became blurred. He lost consciousness soon after reaching home. On admission to the hospital, he had a stiff neck and other signs of meningeal irritation. Spinal puncture showed a bloody spinal fluid. At the time of puncture 2 Gm of sodium sulfapyridine dissolved in 5 cc of water was injected intrathecally. During the injection there were fleeting, repeated flexion movements of the trunk and tremulousness of the lower limbs. Neurologic examination on the second day showed extreme weakness of both lower limbs, there was absence of tactile sensation below the fourth dorsal segment, of pain sense below the third lumbar segment and of temperature sense below the tenth dorsal segment, deep sensibility was absent in the lower limbs, the knee and ankle jerks could not be obtained, there was urinary and rectal incontinence, and the cranial nerves and fundi were normal. The Kahn reactions of the blood and the spinal fluid were mildly positive.

The meningeal signs gradually disappeared. On July 12 examination showed notable improvement in motor power in the right leg, the sensory changes in this leg were gone, on the left there was diminution of sensation below the fourth lumbar dermatome, the sphincter disturbances persisted, there was still tendon areflexia and the spinal fluid was clear.

The author believes that the changes in the spinal cord were due to the intrathecal injection of sulfapyridine.

SAVITSKY, New York

### Peripheral and Cranial Nerves

INJURIES TO THE PERIPHERAL NERVOUS SYSTEM. HOWARD C. NAFFZIGER, *J Nerv & Ment Dis* 101:453 (May) 1945

Failure of functional regeneration of divided nerves depends on many factors including the nature of the nerve (regeneration of nerves of a purely motor or sensory type being better than mixed nerves), the condition of the muscles innervated, the nature of the injury (traction injuries offering a poorer prognosis), the presence or absence of infection and the site of division of the nerve. Injuries near the origin of long nerves require a long time for regeneration. Both experimental and clinical experience support the idea that suture after injury affords the best results provided the wound is clean and free from sepsis. These conditions are not usually met in cases of wartime wounds, so that delayed suture is often necessary. Suture can and should be performed, however, within two or three weeks of healing of the wound. In cases of nerve concussion and partial nerve lesions operative intervention may or may not be required, depending on the degree of improvement and the presence or absence of foreign bodies and persistent pain.

In order to provide the best possible care for victims of peripheral nerve injuries, Naffziger suggests that Army neurosurgical centers caring for patients with such injuries be placed near medical schools, so that experienced civilian neurosurgeons may collaborate in the treatment and opportunities for research may not be lost.

CHODOFF, Langley Field, Va

EFFECT OF SULFONAMIDE DRUGS ON EXPERIMENTAL GUNSHOT WOUNDS OF PERIPHERAL NERVES LOYAL DAVIS, GEORGE PERRET and WALTER CARROLL, War Med 6 228 (Oct) 1944

The incidence of infection in wounds repaired twenty-four to forty-eight hours after injury was reduced from 83.3 per cent, in 6 animals, to 22.5 per cent, in 40 animals, when sulfathiazole jelly was introduced into the wound immediately after its receipt and a sulfonamide drug was powdered into the wound at the time of debridement.

No conclusive evidence was found that regeneration of nerve fibers, formation of axis-cylinders, myelination or absorption of decomposition products of myelin was changed with the use of the sulfonamide drugs. The deviation and abnormal distribution of regenerating nerve fibers were observed regardless of whether a strong mesodermal suture reaction or an epineural reaction was traumatic, infectious or caused by irritation from the sulfonamide drugs. The compounds did not interfere with the neurotization of autogenous or homogenous grafts or with the distal segment. However, in the series of animals receiving homogenous grafts a heteromorphous neurotization of the graft was found in all the animals treated with sulfonamide compounds, whereas similar grafts in untreated animals showed in all instances some degree of isomorphous neurotization.

The authors feel sure that if sulfathiazole jelly were introduced into extensive soft tissue wounds at the time of their receipt, so that all the ramifications of the wound were reached by the jelly, it would be possible to repair divided peripheral nerves at the time the soldier reaches a hospital where the wound could be carefully cleansed, trimmed surgically and sulfonamide drugs powdered into the wound. This would permit the repair of injuries of peripheral nerves at the earliest possible moment consistent with the best surgical treatment of fractures or other accompanying injuries.

PEARSON, Philadelphia

THREE TYPES OF NERVE INJURY H. J. SEDDON, Brain 66 237, 1943

Seddon classifies peripheral nerve injuries as three types: (1) neurotmesis, in which all essential structures of the nerve have been severed; (2) axonotmesis, in which the axons are so severely damaged that complete peripheral degeneration occurs, while the supporting structures of the nerve remain intact; and (3) neurapraxia, in which paralysis occurs in the absence of peripheral degeneration. The morphologic changes associated with neurotmesis and axonotmesis are understood, while those accompanying neurapraxia are unknown. These types of damage to the peripheral nerve may result from a variety of injuries, and the same trauma may produce more than one type of injury. The author studied 650 cases of peripheral nerve injury. Of this group, neurotmesis occurred in 113. Retrograde degeneration occurred in the central portion of the nerve and extended a distance of 1 to 2 cm. Axonal regeneration began almost immediately at the central margin of the degeneration. At the point of injury a hematoma occurred, which was transformed into fibrous tissue. Seddon noted the usual changes of wallerian degeneration in the peripheral stump but emphasized the conspicuous proliferation of Schwann cells at the cut surface, thus he designated as glioma. Frequently the neuroma, composed of scar tissue and regenerating nerve fibers of the central stump, can be felt through the skin. The glioma is rarely palpable. The clinical signs were those of complete interruption of both motor and sensory functions. Spontaneous regeneration was both rare and incomplete.

Seddon studied 81 cases of axonotmesis. In these cases the clinical picture was again that of complete interruption, but recovery was spontaneous. Although recovery was slow, it was, nevertheless, faster than that occurring in cases of neurotmesis after suture of the nerve. The recovery was perfect. In most

instances axonotmesis resulted from blunt injury. Occasionally the injury produced a local swelling of the nerve trunk. In comparing the state of recovery after axonotmesis and that after neurotmesis, Seddon found that after axonotmesis the degree both of motor and of sensory return approached perfection, while after neurotmesis delicate sensory tests, such as two point discrimination, revealed the presence of permanent sensory deficit and motor testing showed that independent and synergic movements were permanently impaired. Seddon concluded that neither infection nor the state of the peripheral portion of the nerve was responsible for this difference in recovery but that the disorganization of the architecture of the nerve attending neurotmesis was the determining factor.

Seddon found three important points in the differential diagnosis of axonotmesis and neurotmesis: (1) the nature of the injury, closed fracture being a more common cause of axonotmesis and open fracture of neurotmesis, (2) the time at which evidence of regeneration should appear spontaneously (if there is no sign of return of function at that time the nerve should be explored), and (3) the appearance of the nerve when exposed at operation.

In cases of neurapraxia Seddon found that motor paralysis was usually complete and greater than the sensory deficit, muscular wasting was slight or not evident, electrical excitability of the muscles was unchanged, recovery of motor function was both rapid and complete, loss of tactile sense was more extensive in area and of greater duration than loss of pain sensation, deep sensation was notably impaired, mild irritative phenomena were common, and the recovery of sensation was rapid.

Seddon studied 36 cases of neurapraxia. In 10 instances the injury was instantaneous, in 13 cases it was due to prolonged compression, and in 3, to intermittent trauma. The average duration of paralysis was about ten weeks. The clinical picture was found to be one of complete motor and incomplete sensory paralysis, the differences between motor and sensory disturbances and in the involvement of various sensory modalities being correlated with the type of fiber mediating these functions and their various susceptibilities to compression. Recovery was spontaneous and complete. At no time was there alteration of electrical reactions.

Seddon emphasizes the occurrence of combinations of the three types of lesions of the peripheral nerves.

FORSTER, Philadelphia

# Society Transactions

## ILLINOIS PSYCHIATRIC SOCIETY

John J. Madden, M.D., Presiding

Regular Meeting, Dec 6, 1945

Peter Bassoe, M.D. DR. PERCIVAL BAILEY, Chicago

This paper was published in the February 1946 issue of the ARCHIVES, page 140

### A Warning Concerning the Use of Curare in Convulsive Shock Treatment of Patients with Psychiatric Disorders Who May Have Myasthenia Gravis DR. LEE M. EATON, Rochester, Minn

Curare has played an interesting role in the history of myasthenia gravis. Realization of the fact that curarization produces a clinical picture resembling myasthenia gravis led Walker (*Lancet* 1 1200 [June 2] 1934) to try its antidote, physostigmine, in the treatment of this disease. She found it effective and soon used neostigmine with gratifying results (*Proc Roy Soc Med* 28:759 [April] 1935). Today neostigmine (prostigmine) is the most effective drug available for the relief of the symptoms of myasthenia gravis.

Bennett and Cash (*ARCH NEUROL & PSYCHIAT* 49 537 [April] 1943), from their experience with curare as a preventive of traumatic complications in convulsive shock therapy, were stimulated to test the sensitivity of patients with myasthenia gravis to curare. They found that the weakness of such patients was greatly intensified by small amounts. Administration of doses only one tenth to one fortieth of those required to produce mild generalized curarization in a normal person resulted in striking exacerbation of symptoms. They then utilized this observation in proposing a diagnostic test for myasthenia gravis (*Dis Nerv System* 4 299 [Oct] 1943, *ARCH NEUROL & PSYCHIAT* 49 537 [April] 1943). From considerable experience with this test, my colleagues and I of the section of neurology of the Mayo Clinic attest to its great value. We find it of particular aid in discriminating between other asthenic states and myasthenia gravis.

Furthermore, this test is helpful in confirming the diagnosis in those patients whose symptoms are so mild that the response to injections of neostigmine is often equivocal. In general, we find that the quinine test (*Proc Staff Meet, Mayo Clin* 18 230 [July 14] 1943) and the curare test are of approximately equal value in excluding or establishing the diagnosis of myasthenia gravis in that borderline group of cases in which the neostigmine test is least reliable.

It may be well to emphasize at this point that the quinine and curare tests should not be used with patients who are seriously weakened, since further weakening may result in death in spite of artificial respiration and administration of massive doses of neostigmine. A tragic personal experience with such a case, in which all the safeguards failed, allows me to speak with authority on this matter.

Experience with curare in cases of myasthenia gravis led me to predict that the ordinary curarization of a depressed patient, preliminary to convulsive shock therapy, might prove fatal should the patient also suffer from myasthenia gravis. Confirmation of the prediction was not made by experience because, fortunately, in the case to be reported the presence of mild myasthenia gravis associated with a depression was recognized before convulsive shock therapy for the depression was begun. A brief account of this case will prove instructive by emphasizing the dangers involved.



## REPORT OF A CASE

A white man aged 36 came to the Mayo Clinic in March 1944 because of exhaustion, insomnia, inability to relax and a fear that he was soon to die. He stated that he worried about everything and admitted having thoughts of suicide. It was learned that for years he had experienced periods of depression, the most intense beginning in February 1938, as a reaction to a change in his work. Within ten months his condition had progressed to a point where he could work no longer as an office manager. As a result, he was confined to psychiatric hospitals for five months. The depressive symptoms became sufficiently mild by the summer of 1939 that he was able to return to work, and within a few months he felt well again.

The patient continued to feel well until the summer of 1943, when he noticed that he could not see clearly unless he held his head far back. Three weeks after he noticed this, diplopia began to occur occasionally and ptosis of the right eyelid became noticeable. At about the same time he began to have difficulty in sleeping, to worry and to feel much as he had during the previous depression. He consulted two neuropsychiatrists, one of whom gave him an injection of neostigmine. The diagnosis of myasthenia gravis was evidently dropped from consideration when the patient reported that after the injection he felt no better.

Examination at the clinic revealed slight psychomotor retardation and thought content appropriate to the depressed emotional state. Neurologic study revealed a moderate degree of ptosis of the right eyelid and considerable weakness of the superior rectus muscle of the right eye and of both anterior tibial muscles. The peroneal muscles and those extending the toes were perceptibly weaker than normal.

The diagnosis of myasthenia gravis on clinical grounds was substantiated when definite strengthening of the weakened muscles occurred after the patient received a subcutaneous injection of 1 mg of neostigmine methylsulfate and when weakening of the muscles occurred after quinine sulfate was administered orally in two doses of 10 grains (0.65 Gm) each two hours apart. Furthermore, 0.2 cc of intocostin, which contains 4 mg of curare, produced a definite weakening effect. This dose is slightly less than one twentieth of the dose that would ordinarily be used preliminary to convulsive shock therapy for a man of his weight (184 pounds [83.5 Kg]).

The diagnosis of manic-depressive psychosis and myasthenia gravis was made. It was suggested that the patient take 15 mg of neostigmine bromide three to five times daily.

The patient returned two months later because of the persistence of psychiatric complaints. Myasthenia gravis was of mild degree, and the patient was well relieved when he was taking neostigmine. From May 26 to June 7, 1944 seven electroshock treatments were administered without preliminary curarization. Four resulted in convulsions. The patient was much improved and returned to work. He relapsed soon, and when he came back for further treatment, four more electrically induced convulsions were given. When he returned home, he refrained from work, at our insistence, for a period of two months. When last heard from, in July 1945, he was well except for ptosis of the right eyelid, which continued to be alleviated when he took neostigmine bromide, and he was successfully engaged in a new occupation.

## COMMENT

Although this patient had myasthenia gravis in its mildest form, he was extremely sensitive to curare, as is usual in such cases. He suffered from a depressive reaction severe enough to warrant electroshock therapy, to which he responded well. Had the associated myasthenia gravis not been recognized and had an ordinary dose of curare been administered as a preliminary to electroconvulsive therapy, death probably would have resulted in spite of heroic measures to combat the effect of curare.

The value of convulsive therapy has become widely established in the treatment of psychiatric disorders, particularly depression. Furthermore, curarization preliminary to convulsive therapy is widely used. Stewart (*Dis Nerv System* 4 236 [Aug] 1943) pointed out that in 1943 more than one hundred institutions in the United States had adopted this plan of treatment. Myasthenia gravis is not nearly so rare as it was once assumed to be. The recognition of milder atypical forms of the disease seems to account for the apparent increased frequency. For many years the diagnosis has been made in approximately 4 out of every 10,000 new cases encountered at the Mayo Clinic. In the last four years I, personally, have examined 175 patients who had myasthenia gravis. In this large group there was no more than an average proportion of major psychiatric disturbances. One patient had a manic-depressive psychosis, 1, a moderately severe reactive depression, 2, reactions resembling those of schizophrenia, with associated exophthalmic goiter, 1, a severe post-traumatic psychoneurosis with paranoid trend, and 1, frank conversion hysteria. Actually, only 2 patients of this group were given convulsive therapy, and for 1 other such treatment was considered. I realize that the specific set of circumstances, that is, a case of unrecognized myasthenia gravis plus associated psychiatric disorder for which convulsive treatment is given after preliminary curarization, rarely will be encountered. However, myasthenia gravis must be ruled out in any case in which curarization is to be used preliminary to electroshock if tragedy is to be avoided. It is hoped that this report may stimulate physicians who use the treatment to consider that myasthenia gravis might be present before proceeding with curarization. To imply that preliminary curarization is to be avoided in the ordinary case in which convulsive therapy is used is not my intention.

#### Psychiatric Overlay in Physical Disease DR LEO KAPLAN, Chicago

This paper was given primarily to point out the many cases of functional overlay that were seen in the Army. The effects of psychogenic factors on physical disease were elaborated on, indicating the relation between psyche and soma. Some of the psychopathologic mechanisms which were apparently responsible for the prolonged delay in recovery from organic disease were pointed out.

A number of cases of organic disease with superimposed functional overlay were presented, including those with such diagnoses as traumatic vasospasm, acrocyanosis, thromboangitis obliterans and motor weakness of various extremities associated with fracture and prolonged application of casts.

The types of treatment and the results were indicated, with formulation of the following conclusions: (1) motivation for production of functional overlay is the same in civilian life as in the Army, namely, gain to the patient by obtaining dependency, attention and security, (2) early recognition and differentiation of that portion of the illness which is functional and that which is organic in order to obtain a better prognosis for recovery, (3) early recognition of functional overlay to prevent chronic invalidism in veterans to be discharged from service.

#### Group Psychotherapy with Private Patients DR ABRAHAM A. LOW, Chicago

A class was started in 1941 with a small group of private patients who met once a week, one patient being interviewed while the others listened. At present the class is attended by upward of 70 patients. The class consists in about equal parts of psychoneurotic and former psychiatric patients.

The discharged psychotic patient suffers from residual symptoms, such as tenseness, difficulty in sleeping, fatigue, numbness, pains, palpitation, blurred vision, head pressure and other sensations, fears and compulsions. These residual symptoms must be relieved without delay. Otherwise, apprehension on the part

of the ex-patient and his relatives creates an unhealthy atmosphere, which may precipitate a relapse

The psychoneurotic patients admitted to the class are chiefly of the chronic type. After making the rounds of physicians and clinics, they have decided they cannot be cured. All they want is a prescription or a "pep talk" for temporary relief. Having discounted the possibility of a final cure, they cultivate a self-appointed defeatism.

The physician is ill equipped to deal with defeatism. To his endeavor to "sell" the idea of mental health the patient offers a sort of "sales resistance." The patient's credo is that the physician would not dare tell the truth even if he knew the condition was incurable. Medical ethics forbids frankness. In class sessions the chronic patient is made to listen to a "colleague" who has successfully "licked" his own chronicity. That colleague is convincing. He has nothing to "sell." The patients attend one weekly class conducted by the physician. In addition, they are encouraged to join the Recovery Association, in which the patients gather in weekly home meetings. There they hold panel discussions, encouraging one another to give up their resistance. This resistance is called "sabotage," because it sabotages the physician's authority. The most pernicious form of sabotage is self diagnosis and self prognosis. If the patient calls his compulsion "unbearable" or his fear "uncontrollable," he pronounces his difficulty serious (diagnosis) and difficult to repair (prognosis). With this, he sabotages the physician's authority.

To check defeatism, the patient must be taught how to curb his temper. Temper precipitates and intensifies symptoms. On the other hand, symptoms give rise to outbursts of temper. A vicious cycle is thus established. This must be broken by class instruction and the self-help activities of the Recovery Association.

The main advantage of the combined class and self-help method is to gain time for the physician. With the aid of various group psychotherapeutic technics it is possible for the physician to reduce the time spent on the individual patient during the office interview. In this manner, group psychotherapy is supplemental to individual psychotherapy.

## NEW YORK NEUROLOGICAL SOCIETY AND NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY

Joseph H. Globus, M.D., *President, New York Neurological Society, Presiding*  
*Joint Meeting, Dec. 11, 1945*

**Presidential Address: Brain Tumor—Its Future in the Light of the Past**  
DR. JOSEPH H. GLOBUS

This paper was published in the April 1946 issue of the *Journal of Neuro-pathology and Experimental Neurology*, page 85, under the title "Brain Tumor—Its Contribution to Neurology in the Remote and Recent Past."

**Suprasellar Calcified Lesion of Unusual Size—Report of a Case**  
DR. ALFRED GALLINEK

An American-born white man aged 35, married, was first examined in October 1944 and has been under observation since that time. At the age of 32 the patient first experienced headaches, which since then have occurred intermittently. The average frequency has been twice a week. The headaches usually begin late in the afternoon. The patient soon discovered that he could eliminate the headache by lying down. He also noticed that he could aggravate the pain by stooping. The headache is always bifrontal and is localized in the orbits behind the eyes and across the bridge of the nose. Recently there have been several episodes of nausea and vomiting, which also were relieved by lying down. For the past two years there have been occasional photophobia and blurring of vision. At the age of 33

the patient experienced the first of a series of "weak spells" These spells occurred infrequently in the beginning, but during the past year he has had seven attacks of loss of tone These attacks were initiated by a sensation of numbness in the forehead and on both sides of the face This sensation was followed by flushing and sweating in these areas Intense weakness then appeared in the legs, and about a minute after the onset of the initial numbness the patient fell to the ground, with perfect preservation of consciousness During the past year the duration of the attacks of loss of tone has been about five minutes from the onset of the first symptoms until the moment when the patient is able to resume standing or walking

Invariably, his headaches have been completely relieved by rest in a recumbent position for about fifteen to thirty minutes His condition has not prevented him from working nine hours a day The past history is noncontributory except for a head injury at the age of 6 years, when he fell out of a cherry tree, hitting his head on a rock He does not recall any details but remembers that he did not have to be hospitalized It is noteworthy that there is no history of polydipsia or polyuria, that the patient's sex life is normal and that he has to shave daily

On examination he weighed 125 pounds (56.7 Kg) and was 5 feet 6 inches (167.6 cm) tall He was of slight body build, no abnormalities were evident on general examination He was right handed Both disks showed slight edema (right eye,  $\frac{1}{2}$  D, left eye, 1 D) There were blurring of the nasal margins and moderate temporal pallor Both visual fields showed marked constriction Visual acuity was 20/30 bilaterally There were hippus and slight nystagmus on left lateral gaze The cranial nerves were otherwise normal except for a slight rigidity of facial expression and vague asymmetry in the innervation of the left side of the mouth, which might represent weakness of the left side of the face of central type Slightly rigid posture was noticeable, particularly on walking An inconsistent tendency toward dorsiflexion of the big toe was occasionally observed on the left, as well as some fanning There was downward drift of the left upper extremity, with convergence and pronation in the right upper extremity The rest of the neurologic status was normal

The initial spinal fluid pressure was 200 mm, after withdrawal of 10 cc the pressure was 170 mm On subsequent spinal punctures, the initial pressure was 130 or 140 mm and the final pressure 70 mm Examination of the spinal fluid showed a total white cell count of 3 per cubic millimeter, a total protein of 160 mg per hundred cubic centimeters, a normal colloidal gold curve and a negative Wassermann reaction The Kline reaction of the blood was negative The urine was normal The blood sugar and the glucose tolerance curve were normal

Posteroanterior and left lateral stereoscopic roentgenograms of the skull showed a large, circumscribed shadow of calcium of almost bony density lying in the suprasellar region, in the midline The inferior margin was relatively straight A small shadow of calcium was seen posterior to this large mass, apparently the posteriorly displaced pineal gland The sella turcica was slightly enlarged The posterior clinoid processes were atrophic The bones of the vault showed no definite abnormalities

The electroencephalogram was normal The basal metabolic rate was -14 per cent The results of other routine laboratory studies were normal

In analysis of this case, the following groups of symptoms are distinguishable: intermittent headaches, to a great extent depending on and relieved by changes in posture, attacks of loss of tone in the lower extremities, vague parkinsonian features in facial expression and gait, a slightly low basal metabolic rate, and moderate papilledema, with constriction of the visual fields and moderate difficulties in vision

The tumor in this case must occupy most of the region of the third ventricle and its adjacent structures Tumors inside the third ventricle are known to produce few symptoms, but for tumors involving the third ventricle as well as adjacent structures Fulton and Bailey have enumerated not less than nine syndromes, most of which were not distinguishable in our case Wilfred Harris stressed the importance of paroxysmal postural headaches as a diagnostic sign of intraventricular

cysts and tumors Stookey described the same type of headache as that seen in the case presented and ascribed it to intermittent obstruction of the foramen of Monro by a neuroepithelial cyst The mechanism of these headaches was explained by Harris as a block of the foramen of Monro Considering the size of the lesion in the case presented, it is likely that compression of and relief of pressure on both veins of Galen play an important role

Attacks of loss of tone were also seen by Harris in a case of colloidal cyst in the foramen of Monro The affective component seen in most cases of idiopathic cataplexy was absent in the case presented

It is difficult to decide whether the lesion in this case is a calcified meningioma (originating from the anterior portion of the falx), a craniopharyngioma or a dermoid It was felt that not much additional information could be expected from air studies and that they might be dangerous The problem of surgical approach was discussed seriously In view of the size of the lesion and its localization, there is no doubt that surgical removal would be difficult The fact that the patient is able to work and to lead a normal life favors a conservative attitude, particularly since all his subjective symptoms usually disappear for about two months after withdrawal of 10 to 15 cc of spinal fluid

The case is presented because of the striking discrepancy between the magnitude of the lesion and the comparatively mild character of the symptoms, as well as the diagnostic significance of postural headaches and attacks of loss of tone

This paper was published in the May 15, 1946 issue of the *New York State Journal of Medicine*, page 1127, under the title, "Postural Headache and Attacks of Loss of Tone in a Case of Calcified Suprasellar Tumor"

#### DISCUSSION

DR H A RILEY This case of Dr Gallinek's has been a subject of considerable interest to us at the Institute Dr Gallinek presented the case at one of our conferences, and we were all in doubt as to the actual nature and possible location of this bony growth There is little for me to discuss in this presentation for Dr Gallinek has covered as adequately as is possible while the patient is still alive the clinical and supposed pathologic features of the situation The two points of interest are those which he emphasized, the attacks and the paroxysmal headaches The attacks are similar to cataleptic seizures but are entirely dissociated from any change in emotional tone That leads me to believe that these attacks may be of cerebellar origin—attacks of cerebellar atony—for some of the neoplasms and lesions of the third ventricle produce predominantly cerebellar symptoms The other feature, which is the presenting symptom in this patient, is the paroxysmal episode of headache Dr Gallinek has emphasized the two explanations for this condition (1) an episodic block of the foramen of Monro and (2) the theory which seems less attractive to me, namely, interference with the veins of Galen At their origin near the foramen of Monro the veins of Galen are very small, and they become large only as they receive successive additions—the vein of the corpus callosum, the vein of the septum pellucidum and the striatal and choroidal veins They assume large proportions only as they pass back to form the great vein of Galen, which with the inferior longitudinal sinus and the basilar veins forms the straight sinus It seems to me that the cause of this intermittent episodic headache, which is positional in character, is much more likely to be blockage of the foramen of Monro, forming a hydrocephalus as a result of the damming back of the cerebrospinal fluid in the ventricular system

I remember a dramatic case of what I thought at first was simple migraine The patient came to me with the complaint of headache, which came on only in episodes, accompanied with some visual phenomena—streaks, jags and lines of light which are frequently associated with ophthalmic migraine His mother and several other members of the family had migraine I kept him under observation for a year or so, treating him, as all try to treat migraine, without any great success About two years after I first saw him, he returned with his headaches materially

increased. He had noticed that they occurred only after he had been studying (he was a student at Princeton), leaning forward over his desk, for a considerable length of time. Only at that time did he show any papilledema, with hemorrhages but no localizing signs. I sent him to the Neurological Institute, where an encephalogram demonstrated beautifully a colloid cyst of the third ventricle. Dr. Davidoff removed the growth by a transfrontal approach, with complete relief of the symptoms and cure of the condition, except that temporarily the patient had a series of convulsions, which were controlled with phenobarbital. I feel that the explanation of this type of headache is to be found in an obstruction of the foramen of Monro.

I believe with Dr. Gallinek that the location of this tumor and its probable origin are in the third ventricle. I think that one may conclude from the roentgenograms that it is too high in the cranium to be a suprasellar craniopharyngioma and too low to have its origin in the anterior portion of the falx, I believe it is too far caudal to arise from the falx, as this membrane arises from the crista galli. It is central in location and occupies the position of the third ventricle, which, if the tumor is so situated, must be greatly dilated.

The other questions of importance in this case concern the advisability of carrying out an air study and of operating. This man is doing fairly well, he has lived for a number of years with this neoplasm, and he probably will live comfortably and productively for a considerable time. I think it is better not to attempt any air studies or operation, a live patient is better than a dead certainty.

Every neurologist who has become accustomed to see cerebral neoplasms recognizes that practically no significance is to be attached to the size of a tumor so far as symptoms are concerned. Those who are entering the field of neurology must appreciate the fact that a tumor makes its presence known primarily, and almost exclusively, by the rapidity of its growth. If a tumor grows slowly, a brain can accommodate itself to the presence of a growth of almost any size, if it grows rapidly, a small tumor may produce serious, and evident and prompt, symptoms.

I wish to congratulate Dr. Gallinek on his careful study and the interesting presentation of this case.

DR. BYRON STOOKEY. I think Dr. Gallinek and Dr. Riley have said everything that is of interest. I am delighted that this patient is Dr. Gallinek's patient and not mine. I should like to thank Dr. Riley for looking at me when he said he would rather have a live patient than a dead certainty. Certainly, I think from the surgical standpoint the patient is better off out of the surgeon's hands. This man is well adjusted to his tumor, since it is calcified, it is no longer growing, he can be followed carefully clinically, and if an operation should be desirable it can be undertaken. I have an idea that the tumor could be removed by heroic measures, perhaps requiring amputation of the frontal lobe. I agree with Dr. Riley and Dr. Gallinek that the growth is probably in the third ventricle, so that an approach can be made if necessary.

Would Dr. Gallinek state what position the patient assumes when he is relieved of his headache? Most patients are relieved, not by lying with the occiput down, but by placing the forehead down. Many a sudden death has been attributed to cardiac disease which was actually due to a tumor of the third ventricle suddenly obstructing the foramen of Monro and producing a rapidly developing hydrocephalus. I think the explanation of obstruction of the ventricular system is the correct one.

DR. ALFRED GALLINEK. In answer to Dr. Stookey's question, the patient has to lie flat on his back to obtain relief from the pain.

#### Phyletic Manifestations and Reversions DR. A. A. BRILL

The author pointed out that both Freud and some of his pupils came to the realization that certain neurotic manifestations cannot be adequately explained by the patient's past but that they can be understood only on the basis of phylogenesis.

The author cited a case of a husband and wife who had lived together for almost a generation, constantly quarreling, separating and fighting. Their behavior was predominantly anal-sadistic, object libido seemed to have played only a minor part in their married existence. The author was struck by the fact that although both husband and wife belonged to a better than middle class cultural level, they continually hurled invectives at each other which referred to the posterior region. As these expressions have always been popular among persons of the lower social strata, it was concluded that they must conceal some long-forgotten pleasant outlets. In other words, the invitation to kiss one's behind, which is now disgusting, must have once formed a pleasant outlet.

The author then examined the biologic development of the penis and vagina and showed that they both stemmed from the anus, that they both developed from the cloaca, and that the rudimentary penis for the transmission of semen only is first encountered in the ornithorhynchus, which forms the link between the three great animal families. This explains why the anal functions still retain some of their erstwhile pleasurable feelings, why many people like to linger and read in water closets or in "comfort stations." They are unconsciously reliving some long-forgotten pleasures. The invitation hurled during fights and quarrels by people of the lower social levels has the same meaning. That these feelings have always existed in concealed form is readily demonstrated by customs and proverbs of primitive and modern peoples and by their occasional outcropping in the literature of the day. The author concludes that the tabooed invitation to kiss one's posterior is a revival of a phyletic engram in distorted form.

#### DISCUSSION

DR EDWARD KEMPF, Wading River, N. Y. Last summer Dr. Brill told me about his patient and his impressions, and I, in turn, told him I had been for several years engaged in an investigation of the evidence on the biology of bisexual differentiation and had found a good deal of information concerning man's recapitulations of the phylogeny of bisexual differentiation in his ancestors. When his paper was announced, I sent him a copy of my paper, so he promptly called me in to discuss his paper at this meeting.

I should like to make a few comments along this line, guided largely by Dr. Brill's interesting material and speculations. I think that the average physician in his education has not been taught to realize the profound importance of ontogenetic recapitulation in the development of man. There is an inclination to think of it as a recapitulation in the embryonic or prenatal stage only, actually, it goes through a long series of steps, which begin with the embryonic stages, including the cloacal differentiations of the anus and urethra, penis and vagina and the hermaphroditic differentiations. All these emerge before birth. After birth, apparently, the cerebral cortex is conditioned by the morphologic and physiologic processes of the organism, as well as by the environment. At birth the cerebral cortex is practically an unconditioned instrument. At this period the infant goes through the differentiation of the oral food-taking and finger-sucking reflexes and of the cystic-urethral-urinary and anal-rectal-defecating functions, combined with a great deal of exhibitionism and learning. It is just beginning to be realized that he should go through these phases, because they are extremely important as foundations for elaborating his future sociability. One finds in dogs, apes and monkeys such behavior in the young animal, which gradually disappears in the adult. The same process seems to occur in man, and all these recapitulations are found in primitive, as well as in civilized, man.

Primitive man is considerably more tolerant toward these functions than is civilized man. Primitive man, like civilized man, usually grades his compliments to another in terms of what is beautiful or good to eat, as favorable terms which reassure the ego and set it up as being socially desirable. He has also grades of defamation, which are identified with poisons and with excreta. These generally,

though not always, mean that the person is identified with the socially outcast. The well-being of the ego is determined by getting plenty of compliments every day from family and neighbors. Every one practices using both sets of identifications. The words used apparently are not particularly significant, it is the tone of voice and the affect with which the things are said that count.

I should like to discuss further this extremely interesting phase of human behavior, but my time limits me to calling attention to the significance of adherence to cloacal interests in children and of the tendency of persons who have been frustrated in society to regress by learning to think of themselves in terms of derogatory, anal-erotic defamations. If one calls a person vile names, and he is not a strong character, he will visualize himself in such terms and will then undergo a great disturbance of affect and physiologic function and a tendency to regression to a lower attitude. Such a condition can become very serious. Take, for instance, the patient with hebephrenic schizophrenia, such a person experiences defeat in the right to live in the heterosexual direction and, finally, a breakdown, with regression to cloacal affects and attitudes. This is largely tied up not so much with constitutional deficiency, for many of these patients recover, as with the pressure of the social group. Treatment often is successful if the patient can be made to think of himself again in better terms, to visualize himself in better terms, such as are pleasant to every one trying to get along in society and be successful. I am sorry that I cannot elaborate further on this extremely interesting paper, but it does perhaps make the point clear that the physician should give importance to the ontogenetic recapitulation of phylogenetic patterns from the cloacal phase all through the genital development.

**Phenomena of Sensory Suppression** MAJOR NORMAN REIDER, Medical Corps,  
Army of the United States (by invitation)

This paper was published in full in the June 1946 issue of the ARCHIVES, page 583

DISCUSSION

DR S BERNARD WORTIS One can add little to the excellent paper Major Reider has given us. This more careful psychologic testing is being used with greater frequency in studying neurologic illness. With such organic lesions of the brain one sees psychologic and somatic factors delicately intertwined. Studies like this emphasize the importance of enlarging the methods and scope of testing in order to pick up these most subtle defects in function. On the neurophysiologic side these data on cortical suppression or extinction have come from the work of Dusser de Barenne, Garrol and McCulloch, and from the clinical side many of these disturbances in function have been described by Goldstein, Schilder, Riddoch, Morris Bender and Furlow. The physiologists have furnished data to indicate that certain areas of the sensory cortex in certain animals, chiefly monkeys, especially areas 4S, 3S, 2S, 8S and 19S, have suppressor strips, and therefore suppressor strip functions, and these can be related to the motor mechanisms. More recently clinicians with war experience have indicated that these reactions are seen in cases of cerebral trauma and that with adequate testing such defects can be elicited. Many a disturbance in function of which soldiers with cerebral injuries complain, although on the surface appearing as a neurotic manifestation, has as a basis injury to cortical areas and gives evidence of definite pathologic localization of the lesion. Moreover, Major Reider has emphasized the homolateral suppressor effect.

The author is to be congratulated on his clinical observations, which further elucidate the psychologic, physiologic and functional factors of cerebral function.

DR E D FRIEDMAN May I ask Major Reider whether he considers these sensory suppression phenomena allied to Babinski's anosognosia?

MAJOR NORMAN REIDER Certainly, it is likely that they are. I think Dr Bender's recent paper (*Extinction and Precipitation of Cutaneous Sensations*, ARCH NEUROL & PSYCHIAT 54 1 [July] 1945) touches on that point.



## CHICAGO NEUROLOGICAL SOCIETY

Ben W Lichtenstein, M D, *President, in the Chair**Regular Meeting, Dec 11, 1945***Paroxysmal Attacks of Unilateral Sweating Associated with a Pontile Lesion Report of a Case DR JOSEPH A LUHAN**

A Negro aged 23 entered Cook County Hospital complaining of a "dead feeling" in the right extremities, blurring of vision and attacks of sweating on the right side of the body associated with dizziness. He had been subject to nocturnal convulsive seizures since the age of 4 years.

About a month before admission, while at work during the day, he suddenly became dizzy and broke out in profuse perspiration on the right side of the body from the head to the toes, inclusive. He went to the washroom to sit down and found that he was unable to wipe the area dry because of profuse sweating. In about twenty minutes the sweating and dizziness stopped. He had had many spells of sweating and dizziness since the first attack, without any of his former "sleeping spells."

Examination on admission disclosed marked diminution of all forms of sensibility on the right half of the body (including the face), right hemiparesis and palsy of the left sixth nerve. He was seen in a number of attacks of profuse sweating on the right side. A roentgenogram of the chest revealed bilateral infraclavicular infiltration suggestive of tuberculosis. Subsequently, there developed conjugate deviation of the eyes to the right, then weakness of the masseter muscle, pronounced deafness and, finally, facial palsy of peripheral type appeared on the left side. The patient died eighty-one days after admission.

Necropsy revealed a solitary tuberculoma confined to the caudal four fifths of the pons, without generalized meningitis, the lesion was secondary to pulmonary tuberculosis.

This case is of interest if for no other reason than the factual observation that paroxysmal hemihyperhidrosis can occur. The patient had had so-called idiopathic epilepsy prior to the development of these attacks of sweating, which were in some way associated with an expanding focal lesion in the left side of the pons, starting probably in the vicinity of the medial lemniscus at about the level of the sixth nerve. It is probable that most of the pontile tegmentum on the right side was intact when the attacks of sweating began.

**Neurologic Disturbances Associated with Multiple Myeloma DR LEROY H SLOAN, DR R W KELTON and DR LOUIS LIMARZI**

Twenty-one cases of multiple myeloma were reported, 11 from the Illinois Central Hospital and 10 from the Research and Educational Hospitals. In 17 of this number the diagnosis had been confirmed by sternal puncture. In 2 cases there was a single isolated myeloma, with a sciatic syndrome in one and a slowly developing syndrome of compression of the cord in the other, in the other cases the lesions were multiple.

The chief complaint was backache, the pain was progressive and severe, radiated anteriorly and was increased by effort, particularly during the act of turning in bed, as well as by coughing, bearing down and local pressure. All levels of the spinal vertebrae were involved. The essential neurologic syndrome was that of compression of the cord, with development of flaccid or spastic paraplegia or quadriplegia, depending on the level of invasion. No isolated cranial nerve palsy was observed. The optic disks showed no evidence of increased intracranial pressure. In 1 case there was deafness due to local conditions not associated with the myelomatous involvement. Convulsive seizures did not occur, even in the presence of extensive destructive changes in the skull. Ascending cystopyelonephritis was the usual cause of death, in several instances true uremia developed.

Laminectomy was of temporary benefit. Roentgen irradiation was the usual treatment for the local process, and blood transfusions were given to combat the anemia which developed as myeloma cells invaded the bone marrow.

Sternal puncture is of maximum importance in diagnosis of lesions of the bony framework, especially when associated with compression of the spinal cord. In 2 cases in this series biopsy completed the diagnosis, but sternal puncture is more valuable when the fluid is examined by one cognizant of cell types and changes. Diffuse areas of rarefaction in bone calls for sternal puncture unless one is certain that a localized primary tumor explains the rarefaction as a metastatic lesion. The diagnosis of localized tumor formation in the spinal vertebrae may be aided greatly by this procedure, even though the tumor appears to be of malignant origin rather than part of an undisclosed multiple, diffuse process. A roentgenogram of the skull will also be of aid, since in multiple myeloma the skull is usually invaded and the characteristic punched-out areas appear, these areas may appear earlier in the mandible than elsewhere in the skull.

The chemical features of multiple myeloma are hyperproteinemia, reversal of the albumin-globulin ratio, hyperglobulinemia and hypercalcemia with normal or high serum phosphorus. The blood picture is that of normocytic or macrocytic anemia, autohemagglutination, frequent leukopenia with atypical plasma cells and myeloma cells and the presence of myeloma cells in the bone marrow. The absence of such cells does not rule out the possibility of multiple myeloma. The neurologic picture is due in most instances to compression of the spinal cord and regional roots, with radiating pain, the pain being made worse on movement, and is associated with gradual development, for example, of paraplegia, quadriplegia, loss of bowel and bladder control.

#### DISCUSSION

DR PERCIVAL BAILEY. I was most impressed with the high incidence of involvement of the spinal cord and the usefulness of spinal puncture in diagnosis. Sometimes it is difficult to make a differentiation, roentgenologically or clinically, of metastatic disease, Hodgkin's disease and myeloma.

DR L. LIMARZI. One of the telltale signs in cases of multiple myeloma is the extremely soft, nonresistant or "cheeselike" consistency of the sternum that is encountered while the needle is being inserted into the sternum for aspiration of marrow for biopsy. This characteristic consistency of the sternum should always make one aware of or suspect multiple myeloma.

DR LEROY H. SLOAN. In the syndrome of compression of the spinal cord one must, of course, consider the likelihood of myeloma. Diagnosis will be greatly aided by sternal puncture and by roentgenograms of the skull and mandible, as well as by the finding of hyperproteinemia with high globulin content and reversal of the albumin-globulin ratio. I wish to thank Dr. Limarzi, who examined all the sternal fluids in this series.

#### Oneriophrenia, a Clinicophysiological Syndrome. DR L. J. MEDUNA and DR W. S. MCCULLOCH

The clinical syndrome called oneriophrenia consists in an oneroid picture, as described by Ragis and by Gross, and a specific disorder of carbohydrate metabolism, indicated by a somewhat sustained level of the blood sugar in the usual glucose tolerance test and in the Epton-Rose glucose tolerance test and by resistance to insulin, due to some factor circulating in the blood and detectable in the urine by bioassay, as indicated in collaborative investigations by Gerty, Urse, Braceland, Vaichulis and their associates. The temporal relations of the psychiatric picture to the biochemical picture were discussed. These observations indicate that the carbohydrate metabolism is disordered during the psychosis and is normal during remissions, spontaneous or induced. There is even evidence that the biochemical changes, as detected in the blood stream, occur about one day before the changes

in clinical symptoms, both on the patient's going into and his coming out of the psychosis

#### DISCUSSION

DR FRANCIS J GERTY It is now known that the "shock" treatments do not give equally good results in all cases of "functional" and "constitutional" psychoses, even when therapy is begun early. Excellent results have been obtained when the initial diagnostic classification has been in the schizophrenic, manic-depressive or unclassified group. If prior to the use of sedation the patient has had evidence of confusion, a better prognosis is generally offered. The use of excessive amounts of sedatives and the effects of near exhaustion from hyperactivity and loss of sleep may interfere somewhat with making a correct judgment as to whether the confusion is a primary or a secondary symptom of the disorder. If the confusion is a primary symptom, one may justifiably believe that pathologic biochemical changes are present which result in a psychotic reaction resembling in some respects the symptoms one associates with schizophrenia, manic-depressive psychosis and other categories of the psychoses. It is in these cases, regardless of the superficial suggestion as to classification along old diagnostic lines, that recovery occurs. If the confusion is merely a secondary phenomenon or is not present at all, the results with shock treatment probably are no better than those without such treatment. If one looks only for the cruder evidences of extreme confusion, one will probably miss detection of many cases that belong in this group. It is unfortunate that there is no better means of detection of these cases than clinical estimate of the mental symptoms. These symptoms represent merely a reaction. Discovery of what lies behind the reaction is still the real problem.

#### Electronic Devices for Use in Modern Neuropsychiatry MR CRAIG GOODWIN

To design apparatus for use in electrophysiology, the engineer must study the problem firsthand to learn what is required of the equipment. Successive revisions of the first design should result in apparatus whose controls are few, orthogonal and stepwise.

One stimulator developed thus uses a variable frequency master oscillator, giving a repetitive, condenser discharge type of stimulus. Other features are a variable coupling condenser, which provides control of wave form, i. e., of the time constant, a three decade voltage divider for control of output, and a degenerative power amplifier with a step-down output transformer. The output is thus of the low impedance, or "constant voltage," type, and its voltage does not vary in response to changes in load or electrical resistance of the preparation. This prevents apparent variations in threshold when pressure of the electrode or the area of contact changes. Finally, the output is obtained from the secondary winding and is thereby isolated from the chassis and from ground. This reduces artefacts and precludes accidental shocks.

In direct current amplifiers preference is given to the method of using a "voltage divider" coupling between stages. This requires a source of voltage above ground and one below. The latter permits the use of a large common cathode resistor to provide differential and push-pull actions, which are generally desirable in biologic amplifiers. The "voltage divider" coupling also makes possible an amplifier whose input and output are each nearly symmetric about ground, standardizing and facilitating interconnections between amplifiers. Thus, a universal low gain amplifier can be used, and two or more may be cascaded if necessary.

The final amplifier should be a single stage, multiple channel amplifier designed simply for the recorder used (crystal or magnetic ink writer or cathode ray, for example). This minimizes retirement of apparatus when recording methods are changed.

## DISCUSSION

DR JAMES G GOLSETH Mr Goodwin has described several measuring instruments which may enable one to learn more about the nervous system. It is not important at this time whether one agrees or disagrees with Mr Goodwin regarding the relative efficacy of a constant voltage, saw-tooth wave as compared with a constant current, square wave for cortical stimulation. It is of great importance, however, that both instruments measure fundamental physical quantities—the former, voltage and time, the latter, current and time. Given such instruments, the investigator may then find out for himself which type furnishes the more accurate data and, in particular, the more reproducible data. In other words, if he correctly employs reliable instruments which measure in a reproducible manner fundamental physical quantities, he may then let the data obtained speak for themselves.

MR JAMES A FIZZELL For the past few years I have been doing work slightly analogous to that of Mr Goodwin, but I do not feel that I am qualified to criticize his work. I am highly impressed with the various pieces of apparatus he has devised, for I can see and appreciate some of the difficulties he has overcome.

It began to appear ten or fifteen years ago that certain fields of medical research would be benefited if electronics could be applied. The field of neurology is a particularly rich one for such application, inasmuch as the nervous system is so strongly analogous to a large communications system. In the development of a modern telephone system, it was necessary to design and build elaborate pieces of test equipment. They were marvelous instruments, but they did not transmit telephone messages, they were only tools. The stimulator and the amplifiers developed by Mr Goodwin are simply tools, regardless of how elaborate they may be.

The first instrument which Mr Goodwin presented might be called a signal generator. It was said to have four desirable features. I am sure Mr Goodwin will admit it has several more, but he has mentioned the principal ones. The amplifier is a test equipment, like a monitor set, which permits tapping in on a telephone line. Application of these pieces of apparatus to the study of the central and peripheral nervous systems is actually to apply them to the greatest of all communication systems.

An outstanding feature of this work was suggested when Mr Goodwin stated that his initial efforts at solving a given problem usually proved to be merely a fixed approximation. His later success came about as a result of cooperation between him and the medical men with whom he worked. The remarkable feature of all these electrical tools is that they are the result of cooperation—the small and powerful diathermy machines, the portable electrocardiographs, the multiple channel electroencephalographs—all are beautiful evidences of cooperation between workers in two highly specialized sciences.

The electronics engineer did not know intuitively that an acceptable input current to an electroencephalographic amplifier would be  $10^{-10}$  microamperes, he found that out by cooperation with medical men. The medical man did not know that reducing the heater temperature of the first stage would reduce emission velocity, noise and grid current while increasing the input resistance, he learned and profited by cooperation with the electronics engineer.

These electronic instruments are wonderful, but taken by themselves they mean very little, because they are simply tools. In order to make the best use of them and to make the greatest advance in neurologic research, it is necessary that workers who use them know something about them and be able to think in terms of them. This means a more complete merger of the two specialized fields of neurology and electronics, which can be accomplished only by considerable study and hard work. I believe that if members of the medical profession learn to use this apparatus correctly, develop an understanding of it and seek more uses for it, there will result a multiplication of such devices, thus speeding advance in neurologic research.

## Book Reviews

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**The Diagnosis of Nervous Diseases** By Sir James Purves-Stewart Ninth edition Price, \$11 Pp 880 Baltimore Williams & Wilkins Company

This is the ninth edition of an excellent work in neurology. The subject is studied from the practical viewpoint of the clinician, with the orientation toward symptoms and syndromes rather than disease entities.

This edition has brought up to date the subject of neurology, with greater emphasis and study on modern methods. The form, printing and illustrative diagrams and photographs are more numerous and discussions are more lengthy and detailed than in the previous editions.

In the preface the author comments on the impact that the recent war has had on neurology and psychiatry. A number of new neurologic syndromes have been revealed, such as the crush syndrome and the visual disturbances of aviators, to mention a few.

The first three chapters deal with physiologic anatomy, and there is an excellent section on methods of case taking. There are chapters on delirium, coma, convulsive disorders, involuntary movements, aphasia and disorders of articulation and a discussion of the cranial nerves.

There are two chapters on pain and other abnormalities of sensation, which are rather comprehensive. There follow chapters on organic paralyses of the upper and lower motor neuron types, recurrent and transient palsies, incoordination, posture and gait, trophoneuroses, reflexes and the vegetative nervous system.

The section on the psychoneuroses and psychoses suffers from the purely organic approach to mental illness and at many points becomes an essay, with sharp criticism of the psychoanalytic theory and method.

The chapters on electrodiagnosis and prognosis, the cerebrospinal fluid and cephalography, disorders of sleep and intracranial tumors are good. There are a useful index and provocative references.

Both elementary and advanced students of neurology will find this book a useful and practical text.

**Our Inner Conflicts** By Karen Horney, M.D. Price, \$2.75 Pp 250 New York W. W. Norton & Company, Inc., 1945

In this book, Dr. Horney continues the elaboration of her ideas of the nature and dynamics of the neurotic character structure, with their challenge to the orthodox, strictly Freudian psychoanalytic concepts, which she elaborated in her previous works. This volume presents the thesis that "the conflict born of incompatible attitudes constitutes the core of neurosis and therefore deserves to be called basic."

It is the dynamic center from which neuroses emanate. Neuroses are an expression of a disturbance in human relationships."

The various methods and techniques which neurotic persons use to attempt to "solve" this basic conflict are then delineated, with Horney's usual lucidity of description and penetration of clinical observation. She classifies these neurotic mechanisms into the following general groups: moving toward people, moving against people, moving away from people, the idealized image and externalization. A vivid picture of neurotic hopelessness as the vault of unresolved conflicts is drawn and a theory of its relationship to sadistic trends suggested.

There is one problem that this book, by its very nature, raises but does not answer, namely: What are the cause and the nature of the disturbance in human relationships that produces the basic conflict and then the neurotic character struc-

tures? This defect is also reflected in the section on the means by which cure is effected in therapy, which, though optimistic, appears vague and general, in contrast to the preciseness and sharpness of the preceding sections

**Shock Treatments and Other Somatic Procedures in Psychiatry** By L B Kalinowski and P H Hoch Cloth Price, \$4.50 Pp 294 New York Grune & Stratton, Inc., 1946

Kalinowski and Hoch have prepared a concise formulation of the results of clinical experience with and experimental work on the shock treatments and other somatic procedures used in therapy. Insulin shock treatment and the convulsive therapies are discussed in detail with regard to organization of treatment, technic, indications and contraindications, complications, medical, psychiatric, psychologic, neurologic, electroencephalographic and neuropathologic observations, prognosis, and results. There follow short chapters on other pharmacologic and physical therapies and on prefrontal lobotomy. A review of theoretic considerations concludes the text.

From a thorough knowledge of the extensive literature and a wide experience in the field, the authors have prepared this authoritative, well organized, lucid discussion of the subject. Controversial matters are objectively presented, and the authors' position is briefly stated. For details the reader is referred to the extensive bibliography. The authors take the position that the shock therapies properly applied in time are effective in many cases of schizophrenia and in the affective psychoses. Adverse reports in the literature are critically evaluated, and detailed recording of the type of case material, technic and end results is urged in future work.

The authors, however, are frank to confess that "we are treating empirically disorders whose etiology is unknown with shock treatments whose action is also shrouded in mystery."

This volume should prove useful as an introduction to these therapies for students and physicians. It is a good reference work for psychiatrists who are advising or applying shock treatment.

**The Biology of Schizophrenia** By Roy G Hoskins Pp 191 Price, \$2.75 New York W W Norton & Company, Inc., 1946

The material in this book is a slightly amplified version of the Salmon Memorial Lectures delivered by Dr Hoskins in 1945. In this book the author has summarized his viewpoint. It is essentially a call to the medical profession not to neglect the retort and microscope in the deluge of the facile and seductive psychoanalytic approaches to mental disease.

In the first section, the author traces the development of man from an isolated atom to his present integrated self in society—quite an optimistic undertaking for sixty-seven pages! No issue is taken with the author's statements, but one wonders what his purpose was in initiating a review of so vast a subject, which of necessity had to be brief and which for the most part is known to the average scientific reader. For example, he allots exactly five brief pages to a subject he heads "The Nature of Man."

In the second section, he describes schizophrenia, again in such a brief manner that it suffers from underdescription. The inability to "empathize" is the psychologic core of the schizophrenic process. However, the author believes that schizophrenia is definitely a disease entity and that the substratum is an organic one. With this view in mind, he has conducted many years of investigation particularly on the endocrine system. His own work and the work of others are briefly summarized in the last section. Research has attacked the schizophrenic patient from the vestibular canals to his vitamin tolerance. Metabolism, circulatory differences and the endocrine glands, individually and collectively, have been studied. No conclusions of any significance have as yet been drawn. But

the author is exceedingly optimistic. He sincerely believes that the solution lies in a qualitative and quantitative refinement in methods of investigation.

The book suffers from brevity, albeit the promising nature of the title. Schizophrenia in its biologic setting is but postulated. Its proof in this book goes begging. The volume is recommended as an important contribution to the subject.

**Principles of Dynamic Psychiatry** By Jules H. Masserman, M.D. Pp. xiv, plus 322. Price, \$4. Philadelphia: W. B. Saunders Company, 1946.

In this book, the second in a series of three (or more), Dr. Masserman intends to make clear to the student the mass of material rapidly accumulating which is being organized into what is known today as dynamic psychiatry. He succeeds well in the first part of the book, in which he discusses the development of behavioral theories, from the behaviorism of Watson to the psychoanalysis of Freud and the psychoanalysis as it is practiced today. The Gestalt conceptions, the Meyerian psychobiology, the Adlerian schools, the Horney group (albeit briefly dismissed), the Pavlovian reflexology and the descriptive formulations of Krapelin and Bleuler, all are discussed and criticized. Dr. Masserman pays his respects to all of them but calmly drops small fragmentation bombs in their midst, picking up some of the pieces and emerging with his own "biodynamic formulations of behavior," which is his concept of the true dynamic psychiatry.

He proceeds by setting down a set of criteria which he believes psychiatry should attempt to fulfill if it wishes to be classed among the sciences. Therefrom spring his four principles of dynamic psychiatry: (1) principle of motivation, (2) principle of experimental interpretation and adaptation, (3) principle of deviation and substitution and (4) principle of conflict. But that is not all. Based on his experimentation (briefly summarized in this book but extensively presented in his volume "Behavior and Neurosis," published in 1943), he has evolved at least five corollaries to each principle.

The author says of his own formulations that they "fall far short of covering all the phenomena of behavior and their possible interrelationships." However, the reviewers believe that his biodynamic formulations are instructive, stimulating and, above all, provocative of further thought, study and, especially, experimentation. Without doubt, the author will welcome any changes or regrouping of his formulations provided such are based on biodynamic principles of study. If he does not have the answer now, he has certainly opened a new road to research in psychiatry, which he invites all to travel with him. The "principles" as presented in this volume are not as fully developed as one would like, and it is hoped that the author's "Practice of Dynamic Psychiatry," now in preparation, will supply the integration, making his formulation more dynamically applicable to clinical material.

A serious criticism of a book of this kind intended for students is that it suffers from the complicated language used. Words such as solipsism, eschatologic, paranoid, epinosis, ecdemomania, ecdysiasm, eleutheromania, eutelegensis, gelasmus, hetairism, hyponoia, komotropy, letheomania, misocania, pleniloquence, pleonemia and ululation do not add to quick understanding of ideas. On the other hand, the case illustrations and the illustrative psychoanalysis of a neurotic personality are very useful in elucidating the text.

The next book in the series is anticipated, but a change in the semantic style is recommended.

## EFFECT OF GLUTAMIC ACID ON MENTAL FUNCTIONING IN CHILDREN AND IN ADOLESCENTS

FREDERICK T ZIMMERMAN, M D

BESSIE B BURGEMEISTER, Ph D

AND

TRACY J PUTNAM, M D

NEW YORK

THE PRESENT experiment is designed to investigate the effect of *l* (+)-glutamic acid on mental functioning in human subjects and is an outgrowth of a recent study by Zimmerman and Ross<sup>1</sup> on the effect of glutamic acid on maze learning in the white rat. In that experiment 200 mg of glutamic acid was added to the diet of normal white rats for two weeks and its administration continued during the period of training. It was found that the glutamic acid group learned a simple maze much faster than the control group. In fact, the total number of trials required to learn was less than half that taken by the controls. The results were statistically significant in terms of time and accuracy scores, as well as in number of trials required to master the maze. The enhancement of learning was sufficiently striking to warrant an experimental investigation in the clinical field, especially since Price, Waelsch and Putnam,<sup>2</sup> in reporting on the incidence of petit mal and psychomotor seizures, observed a "universally increased mental and physical alertness" in the patients treated with glutamic acid and noted that the "degree of improvement in mental efficiency could not be correlated with the incidence of seizures."

The above mentioned experiments on the simple maze also suggested to Albert and Warden<sup>3</sup> the possibility that adding *l* (+)-glutamic acid

The expenses of this investigation were defrayed in part by a grant from the Commonwealth Fund, supplemented by a grant from the Putnam-Salzer Gift.

From the Department of Neurology, Columbia University College of Physicians and Surgeons, and the Department of Psychology, Neurological Institute of New York.

1 Zimmerman, F T, and Ross, S. Effect of Glutamic Acid and Other Amino Acids on Maze Learning in the White Rat, *Arch Neurol & Psychiat* **51**: 446-451 (May) 1944.

2 Price, J C, Waelsch, H, and Putnam, T J. *dl*-Glutamic Acid Hydrochloride in the Treatment of Petit Mal and Psychomotor Seizures, *J A M A* **122** 1153-1156 (Aug 21) 1943.

3 Albert, K E, and Warden, C J. The Level of Performance in the White Rat, *Science* **100**.476 (Nov 24) 1944.



to the normal diet might enable white rats to learn more complex problems as well. These investigators, using a problem box,<sup>4</sup> found that supplementing the normal diet with *l* (+)-glutamic acid did cause white rats to advance further in a series of increasingly difficult problems.

#### MATERIALS AND METHODS

*Choice of Patients*—The patients in this study form only a fractional part of the larger experiment now in progress, but results so far obtained seem to justify a preliminary report. The larger group includes children and adolescents who are mentally retarded or have convulsive disorders. The patients were selected by both neurologic and psychologic criteria. Neurologically they were selected so as to avoid, as nearly as possible, complicating organic features. This, however, could not be done in every instance, especially in the group with convulsive disorders. Psychologically, they were selected so as to obtain the effect of glutamic acid on mental ability in all age groups from childhood to adolescence at various intellectual levels. Seven of the 9 subjects completing the experiment are patients with convulsive disorders. Two are mentally retarded without convulsions.

The control group was selected primarily to ascertain the effect of control of seizures for varying periods of time on intelligence. Experiments on 9 subjects have been completed.

*Dosage*—After neurologic examination and appropriate laboratory studies, an initial psychometric test was performed. Glutamic acid was then administered in gradually increasing doses. The dose was increased to the point where increased motor activity was apparent. This dosage was then maintained or reduced, depending on the degree of motor activity evoked. The criterion of increased motor activity was used, since this effect on rats was uniformly observed in the maze experiment.

Since much of the acid is lost by metabolism in the liver, by transamination and by competition of the various organs of the body for this essential amino acid, the effective dose must be determined empirically for each individual patient. The dose may range from 6 to 24 Gm per day, but on the average 12 Gm is sufficient. It is administered orally in tablet, powder or capsule form. Gastric distress is occasionally observed, but this can usually be obviated by discontinuing treatment for a few days and then beginning with smaller doses, which are gradually increased as tolerance develops. Table 1 shows the amount of glutamic acid given to each patient in the experimental group, as well as the data on reduction of seizures.

*Methods of Testing*—The patients were tested at the beginning and end of a six month period in which they received glutamic acid therapy. They ranged in age from 16 months to 17 1/2 years, so that different measuring instruments were required for different age levels, as well as separate treatment of data. Prior to glutamic acid therapy, 6 of the group were given the Stanford-Binet intelligence test, form L, 1937 revision<sup>5</sup>, 1 was tested with the Wechsler-Bellevue scale<sup>6</sup>,

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4 Warden, C J, Jenkins, T N, and Warner, L H. *Comparative Psychology*, New York, The Ronald Press Co, 1935, vol 1, pp 350-354.

5 Terman, L M, and Merrill, M A. *Measuring Intelligence*, New York, Houghton Mifflin Company, 1937, p 461.

6 Wechsler, D. *The Measurement of Adult Intelligence*, Baltimore, Williams & Wilkins Company, 1939.

2 were given the Kuhlmann-Binet test <sup>7</sup>, 5, performance tests (Arthur point scale <sup>8</sup> or the Merrill-Palmer test <sup>9</sup>), and 7, the Rorschach ink blot test <sup>10</sup>. Retests with the same battery were made after the six month interval.

## RESULTS OF TESTS

Table 2 shows the results of the Stanford-Binet test

TABLE 1—*Data on Medication and Reduction of Seizures in the Experimental Group*

Case No	Diagnosis	Duration of Disorder on 1st Test	Number of Seizures		Medication
			Before Medication	Reduced to	
1	Idiopathic petit mal	8 yr	1 per day	None	Phenobarbital, 0.06 Gm t i d, glutamic acid, 2 Gm, increased to 4 Gm t i d
2	Idiopathic petit mal	2 yr	7-9 daily	1-2 daily	Glutamic acid, 4 Gm t i d
3	Idiopathic grand and petit mal	3½ yr	Petit mal 10-14 per week, grand mal 1-2 per week	None	Diphenylhydantoin, 0.1 Gm (per day, changed to methyl phenylethylhydantoin, 0.1 Gm q i d glutamic acid 4 Gm t i d
4	Nonconvulsive disorder—mental retardation				Glutamic acid, 2 Gm t i d, increased to 4 Gm t i d, then reduced to 3 Gm t i d
5	Idiopathic grand mal	9 yr	1 every 3-4 mo	Same frequency, less severe	Diphenylhydantoin, 0.1 Gm b i d, phenobarbital, 0.03 Gm t i d, glutamic acid 4 Gm, increased to 6 Gm t i d
6	Idiopathic grand and petit mal	6 yr	1 per day	None	Diphenylhydantoin, 0.1 Gm b i d, phenobarbital, 0.03 Gm b i d, glutamic acid, 2 Gm, increased to 8 Gm, t i d
7	Idiopathic grand mal	4 yr	1 per mo for 1 yr, free past 3 yr	None	Diphenylhydantoin, 0.1 Gm t i d, phenobarbital, 0.03 Gm t i d, glutamic acid, 2 Gm, increased to 4 Gm t i d
8	Nonconvulsive disorder—mental retardation				Glutamic acid, 2 Gm, reduced to 1 Gm, increased to 4 Gm t i d
9	Idiopathic grand mal	10 mo	From 10-14 daily to 1 per day	None	Phenobarbital 0.03 Gm o d, glutamic acid, 2.5 Gm t i d

One subject (case 7), aged 16 years 5 months at the time of the first test, was tested with the Weschsler-Bellevue scale,<sup>6</sup> and the results appear in table 3

7 Kuhlmann, F A Handbook of Mental Tests, Baltimore, Warwick & York, Inc., 1922

8 Arthur, G A Point Scale of Performance Tests, New York, The Commonwealth Fund, 1930

9 Stutsman, R Mental Measurement of Preschool Children, Yonkers-on-Hudson, World Book Company, 1931

10 Rorschach, H · Psychodiagnostik, Berne, E Bircher, 1921

Results of the performance tests are given in table 4

Rorschach records were obtained from 7 of our 9 subjects before and after treatment with glutamic acid, and the results revealed increased productivity following the six month interval in all cases Technical

TABLE 2—*Ages and Scores on Stanford-Binet Intelligence Test of Experimental Group*

Case No	Age at First Test	Intelligence Quotient	
		First Test	Retest
1	10 yr 2 mo	131	138
2	4 yr 5 mo	115	127
3	5 yr 1 mo	67	72
4*	17 yr 7 mo	57	64
5	13 yr 8 mo	47	56
6	12 yr 10 mo	45	54

\* The patient had a nonconvulsive disorder

TABLE 3—*Results of the Wechsler-Bellevue Test*

	Initial Test	Retest
Full scale quotient	107 (average)	120 (superior)
Verbal quotient	106	116
Performance quotient	105	119
Subtests		
Information	11	11
Comprehension	11	11
Arithmetic	12	17
Digits	9	9
Similarities	8	11
Vocabulary	13	13
Picture completion	10	10
Picture arrangement	12	17
Object assembly	9	11
Block designs	10	13
Digit symbols	13	14

TABLE 4—*Changes in Mental Age on Performance Tests in Experimental Group*

Case No	Test	Mental Age, First Test	Mental Age, Retest After 6 Mo
1	Arthur	10 yr 11 mo	15 yr 8 mo
2	Merrill Palmer	4 yr 3 mo	6 yr 4 mo
3	Merrill Palmer	3 yr 1 mo	3 yr 11 mo
4	Arthur	7 yr 0 mo	8 yr 10 mo
5	Merrill Palmer	3 yr 11 mo	4 yr 7 mo

difficulties of interpretation prohibit our including a detailed analysis of the records in this paper, this will be dealt with in a report on the large experiment now in progress It seems worth while, however, to include a sample record (case 3) here, in order to illustrate that the

retest records were characteristically more dynamic than the initial records and suggested basic changes in the personality structure

Rorschach Record 1 Initial Test Intelligence quotient 67 Age 5 yr 1 mo			Rorschach Record 2 Retest Intelligence quotient 72 Age 5 yr 7 mo		
Card No	Seconds Before Response	Response	Card No	Seconds Before Response	Response
I	4	A boat	I	7	Two men
II	2	A boat	II	5	A tree—no—I have a Christmas tree—two red firemen (inquiry)—here is the driver (points to right side)—and here's the fellow that rides on the back (points to the left side)
III	2	A boat	III	8	I don't know Two little ducks swimming
IV	1	A boat	IV	17	I don't know A tail—a pussy cat's tail
V	1	A boat	V	12	I don't know An Indian
VI	3	A boat	VI	6	A cross
VII	2	A boat	VII	17	I don't know Two little Indians fighting
VIII	1	A boat	VIII	5	A Christmas tree
IX	3	A boat	IX	6	Two little Indians
X	2	A boat	X	3	A Christmas tree

In cases 8 and 9 the Kuhlmann-Binet test<sup>7</sup> was required because of serious retardation

CASE 8—The chronologic age at the time of the first test was 2 years. A basal mental age of 3 months was established, all tests for the six month level being creditable except for reaction to source of sound. In tests at the 1 year level sitting unsupported and imitation of movement constituted the child's highest successes. As scored, her performance rated 8 months.

A retest after a six month period revealed a basal mental age of 6 months. No credit for speech was possible, although she then had a better understanding of words. A striking improvement in the motor field was seen in her ability to walk with help and to lower herself from a standing to a sitting position, although she did the latter in an awkward manner. Her highest successes now consisted in cooperation in dressing, as she held out her arm when attempts were made to put on her coat, recognized objects and spit out solids, according to report. As scored, her performance on the retest rated 14.4 months, which is a gain in mental age of slightly more than 6 months in a six month interval, a normal rate of development.

CASE 9—Chronologic age at the time of the first test was 16 months. On the Kuhlmann-Binet material, carrying the hand or object to the mouth, reacting to sudden sounds and binocular coordination were creditable at the 3 month level. The child's highest questionable reaction was to source of sound at the 6 month level. His total performance measured just short of the 3 month level.

Retests six months later showed creditable results in all tests at the 3 month level. In tests at the 6 month level, balance, source of sound and use of the opposing thumb earned credit. The most noticeable feature was the child's ability to walk alone and to sit alone. These earned credit at the 1 year level. According to report, he was also said to spit out solids, a performance giving him credit at the 18 month level. His total performance now rated 7.2 months and represented a gain in mental age of more than 4 months in an interval of six months.

## EFFECT OF CONTROL OF SEIZURES ON INTELLIGENCE

Seven of the 9 subjects completing the experiment are patients with convulsive disorders, and 2 are mentally retarded without convulsions. Such a sample, consisting almost entirely of patients with convulsive disorders, presents a special problem in estimating the effect of glutamic acid on mental functioning, since it raises the question whether control or reduction of seizures may result in an increase in psychologic test scores.

Several statistical studies which have appeared fail to demonstrate a positive relationship between reduction in number or severity of seizures with anticonvulsive medication and increase in intelligence quotient on the Stanford-Binet test. Much of the work done has concerned itself with the problem of mental deterioration and its arrest under drug therapy. Dawson and Conn,<sup>11</sup> Kugelmass, Poull, and Rudnick,<sup>12</sup> and others reported that children showed a decrease in intelligence quotient scores if medication failed to decrease the number and severity of seizures but did not establish the fact that reduction or control resulted directly in an increase of scores.

Yacorzynski and Arieff,<sup>13</sup> in studying 63 patients with "nonorganic epilepsy," subjected 49 to bromide therapy over a period of six months to five years, gave 9 phenobarbital from one to four years and kept 5 without medication. Fourteen of the patients were under 16 years of age. All patients were given the Stanford-Binet test two to four times during an interval of one to seven years. The authors concluded that changes in individual scores are not associated with bromide treatment and that "there appears to be no relationship between the reduction in the number or severity of seizures and the changes of the intelligence quotients."

Similar findings were reported by Fetterman and Barnes<sup>14</sup> in their study of 46 adult patients under phenobarbital therapy who were retested with the Stanford-Binet scale after two years, the data suggesting that "the intelligence quotient is not materially altered by the continued use of sedative drugs." Collins<sup>15</sup> also concluded that phenobarbital has little effect on intelligence.

11 Dawson, S, and Conn, J C M. The Intelligence of Epileptic Children, *Arch Dis Childhood* 4 142-151, 1929

12 Kugelmass, I N, Poull, L E, and Rudnick, J. Mental Growth of Epileptic Children, *Am J Dis Child* 55 295-303 (Feb) 1938

13 Yacorzynski, G K, and Arieff, A J. Absence of Deterioration in Patients with Nonorganic Epilepsy with Especial Reference to Bromide Therapy, *J Nerv & Ment Dis* 95 687-697, 1942

14 Fetterman, J, and Barnes, M R. Serial Studies of the Intelligence of Patients with Epilepsy, *Arch Neurol & Psychiat* 32 797-801 (Oct) 1934

15 Collins, A J. Psychometric Records of Institutionalized Epileptics, *J Psychol* 11 359-370, 1941

Ross and Jackson<sup>16</sup> reported on the effect of diphenylhydantoin given to a series of 73 patients, ranging in age from 11 to 51 years, 29 of whom had a disorder diagnosed as idiopathic epilepsy. These patients received 0.1 to 0.5 Gm of diphenylhydantoin sodium daily over an interval of twelve to eighteen months and were tested and retested with the Stanford-Binet scale. In 65 per cent of the group seizures were reduced 75 per cent or more, and the authors stated

One might expect that with the heightening of interest, initiative, and alertness shown by many of the patients, their intelligence ratings would be raised. They actually give the impression of being more intelligent than at the beginning of treatment. However, this appearance is deceptive, for there obtained practically a balance between raised and lowered intelligence ratings in the face of equivalent seizure reduction.

Performance tests (the Arthur scale) were also given, and results were more striking.

Performance ratings were raised appreciably in a small percentage of patients. The drug seemed to have a greater beneficial effect in this capacity than on intelligence.

Peoples and Tatum<sup>17</sup> found no significant change in the intelligence of 12 morons and idiots treated with diphenylhydantoin, but 5 showed gains in the motor field and improvement in general behavior.

It seems necessary to accept with reservations some of the evidence from the literature for groups which include adults because of the questionable validity of intelligence "quotients" so obtained with the use of the Stanford-Binet scale on adult groups. Since the Stanford-Binet scale assumes a linear relationship between chronologic age and mental age, which does not hold for adults, it appears wiser to substitute "score" for "intelligence quotient" in interpreting results of tests for adults. Nevertheless, the same lack of improvement in retest scores does seem to be indicated among adults as is found among children with convulsive seizures which are controlled or reduced by medication.

*Control Group*—As a check on the findings of other investigators and on the results for the present experimental group, clinic children and adolescents are being studied who were tested before and after a period in which convulsive seizures were controlled or appreciably reduced by medicaments other than glutamic acid. To date, 9 such children have been studied, and data obtained from this control group are presented in table 5.

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16 Ross, A. T., and Jackson, V. Dilantin Sodium. Its Influence on Conduct and on Psychometric Ratings of Institutionalized Epileptics, *Ann Int Med* **14**: 770-773, 1940.

17 Peoples, S. A., and Tatum, A. F. Dilantin Sodium Therapy in Deteriorated Epileptics Refractory to Other Treatment, *J M A Alabama* **12**:197-199, 1943.

For 1 subject only was the intelligence quotient raised (1 point), whereas for 7 of the 9 subjects a decrease in score occurred, as is shown in table 6. Even though the control group is a small one, the data certainly do not suggest that an increase in the intelligence quotient

TABLE 5—*Data on Reduction of Seizures in the Control Group*

Case No	Diagnosis	Duration of Disorder on First Test	Number of Seizures		Medication
			Before Medication	Reduced to	
1	Idiopathic grand mal	3 mo	1 per hr	None for 5 mo	Diphenylhydantoin, 0.06 Gm t i d
2	Idiopathic focal motor cortical seizures	7 yr	2-6 per mo	None for 1 yr	Phenobarbital, 0.015 Gm t i d
3	Idiopathic grand mal	3 yr	Series	None for 4 yr	Phenobarbital, 0.03 Gm b i d, diphenylhydantoin, 0.03 Gm per day
4	Idiopathic grand and petit mal *	6 yr	1-3 grand mal daily, 10-200 petit mal daily	No grand mal for 1 yr, petit mal, 1-2 daily	Phenitoin, 2 Gm q i d
5	Idiopathic petit mal	5 mo	10-15 daily	None for 11 mo	Phenobarbital, 0.015 Gm t i d
6	Idiopathic petit mal	1 yr	3-6 daily	None for 2 yr	Diphenylhydantoin 0.1 Gm t i d
7	Idiopathic grand and petit mal	5 yr	4-7 grand mal daily, 10-15 petit mal daily	None for 3 yr	Diphenylhydantoin, 0.1 Gm t i d, phenobarbital, 0.03 Gm t i d.
8	Idiopathic grand mal	3 yr	10-15 a mo	None for 11 mo	Phenobarbital, 0.1 Gm per day
9	Idiopathic grand and petit mal	6 yr	6 grand mal and petit mal daily	No grand mal for 3 yr, no petit mal for 6 mo	Diphenylhydantoin, 0.1 Gm t i d

\* A severe organic condition is also present

TABLE 6—*Age and Intelligence Test Scores of Control Group*

Case No	Age at First Test	Date				Intelligence Quotient	
		First Test		Second Test		First Test	Second Test
1	8 yr 0 mo	October	1945	March	1946	110	110
2	5 yr 5 mo	December	1936	May	1941	102	99
3	6 yr 3 mo	September	1941	March	1946	93	90
4	7 yr 4 mo	October	1942	May	1943	93	72
5	6 yr 11 mo	June	1943	March	1946	90	74
6	7 yr 11 mo	October	1943	February	1946	86	76
7	12 yr 0 mo	January	1943	October	1943	71	64
8	9 yr 0 mo	November	1944	March	1946	70	71
9	8 yr 11 mo	March	1942	January	1946	56	53

accompanies reduction of seizures. Our results, therefore, agree substantially with others reported in the literature.

*Evaluation of Experimental Results*—The results given in table 2 are in striking contrast to those obtained for the control group (table 6), since in every instance a definite increase in the retest intelligence quotient appears in the experimental group. Some of the change may be accounted for in terms of practice effect, although it is believed that this

is negligible, and some in terms of variability in retest scores. Variability, however, is just as likely to produce a lowering in the individual retest score as it is to result in a higher quotient. Ross and Jackson<sup>16</sup> pointed out that a gain of 10 points or more in the retest quotient of 6 of their 73 patients was offset by a loss of 10 points or more in the quotient of 4 other patients. Because chance fluctuations tend to balance each other in this way, little change in the average intelligence quotient for a group is to be expected from chance factors. For all their 63 patients, Yacorzynski and Arieff<sup>13</sup> obtained an average shift in the intelligence quotient of only 1.3 points, which is not significant. Their findings are similar to those of other investigators, showing only small differences in retest scores and do not reveal a consistent trend in a positive direction, as do our retest intelligence quotients.

TABLE 7—*Dispersion of Retest Scores on the Stanford-Binet Test\**

Intelligence Quotient	Probable Error of Intelligence Quotient, Points	Four Times Probable Error of Intelligence Quotient, Points
130 and over	3.54	14.16
110 - 129	3.29	13.16
90 - 109	3.04	12.16
70 - 89	2.60	10.40
Below 70	1.49	5.96

\* After Terman and Merrill<sup>5</sup>

TABLE 8—*Changes in Intelligence Test Scores of the Experimental Group Given the Stanford-Binet Test*

Case No	First Intelligence Quotient (Average 77)	Retest Intelligence Quotient (Average 85)	Point Change + -	Chances of a Significant Difference
1	131	138	7	80 in 100
2	115	127	12	98 in 100
3	67	72	5	97 in 100
4*	57	64	7	100 in 100
5	47	56	9	100 in 100
6	45	54	9	100 in 100

\* This patient had a nonconvulsive disorder

In evaluating test reliability, level of intelligence is a potent factor. Terman and Merrill<sup>5</sup> have shown that the dispersion of retest scores on the Stanford-Binet test increases with the higher intelligence quotients, as shown in table 7. This means there is practical certainty that a variation of 14.16 points or more would not occur by chance for a subject with an intelligence quotient of 130 or more, or one of 5.96 points or more for a subject with an intelligence quotient of 70 or below.

Analysis of our data according to the Terman and Merrill criteria is presented in table 8.



It may readily be seen from table 8 that for the group our data yield an average increase of 8 points in intelligence quotients on retest, with no negative deviations whatsoever. Of special importance is the fact that for the subjects with the three lowest initial scores, one of whom has a nonconvulsive disorder, statistically significant differences in retest quotients are indicated. Higher quotients would least be expected for persons with this degree of retardation, since under ordinary conditions the discrepancy between chronologic and mental age tends to grow wider as chronologic age increases and more often results in a lowering of the intelligence quotient.

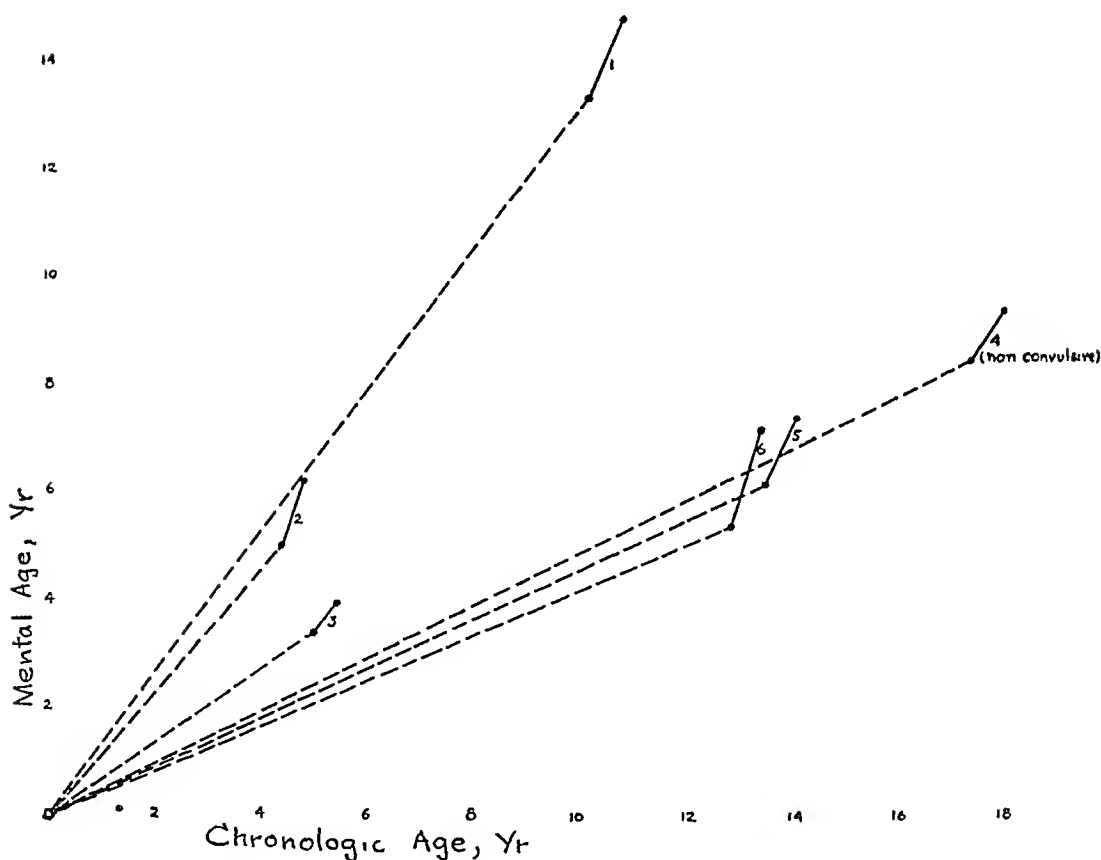


Fig 1—Relation of mental age to chronologic age before and during glutamic acid therapy for 5 patients with convulsive disorders and 1 patient with a non-convulsive disorder as shown by verbal test scores. The previous rate of development is shown by the broken line, the rate during therapy, by the solid line.

Impressive as are these changes in intelligence scores, their significance becomes even clearer when they are viewed as ratios of mental age to chronologic age (fig 1).

For all subjects, sharp, positive increments in mental ages are apparent after treatment with glutamic acid with the mental ages of the

low grade subjects increasing at a rate faster than is expected in children of average intelligence (fig. 2).

Table 6 shows a positive change of 13 points in the full scale Wechsler-Bellevue quotient, with some gains on both verbal and performance sections, results being consistent with those obtained on the Stanford-Binet tests. Consistent increases in individual performance scores are apparent, without negative deviations, as they are on the verbal intelligence test material. Some gains would, of course, be expected, because the group is older on retest. If, however, the scores are considered

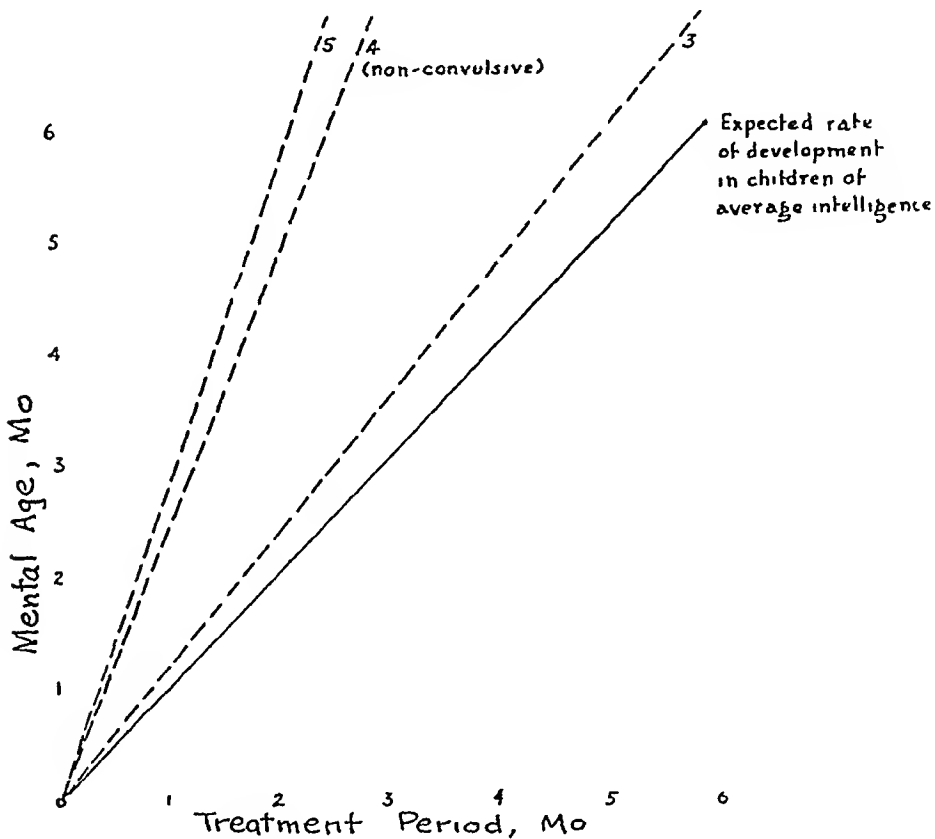


Fig 2—Increment in mental age during glutamic acid therapy in 3 mentally retarded children, 2 of whom had convulsive disorders, as shown by verbal test scores. Subject 3 made a gain in mental age of 7 months, subject 4, a gain of 14 months, and subject 5, a gain of 16 months, in a six month experimental period. The expected rate of development (shown by the solid line) in children of average intelligence is 6 months in a six month period.

in connection with chronologic age (fig 3), more than the normally expected rate of increase is maintained, and more than in the case of the verbal intelligence test material.

In the control group, however, a slight gain in retest performance scores is also indicated, and it is believed that in both groups reduction of seizures may account for some of the improvement found on motor tests.

As shown in the first Rorschach record in the case cited, little relationship exists between concept and blot for any of the cards, responses being typical of very young children, who frequently show perseveration on an idea which seems acceptable to them. In contrast to this, the responses of the second record are of very good form quality and without exception fit the contour of the blot material. While the retest records of all subjects in our experimental group do not show such striking improvement as does that in the case cited, each is definitely more productive. This suggests that glutamic acid has an effect on mental func-

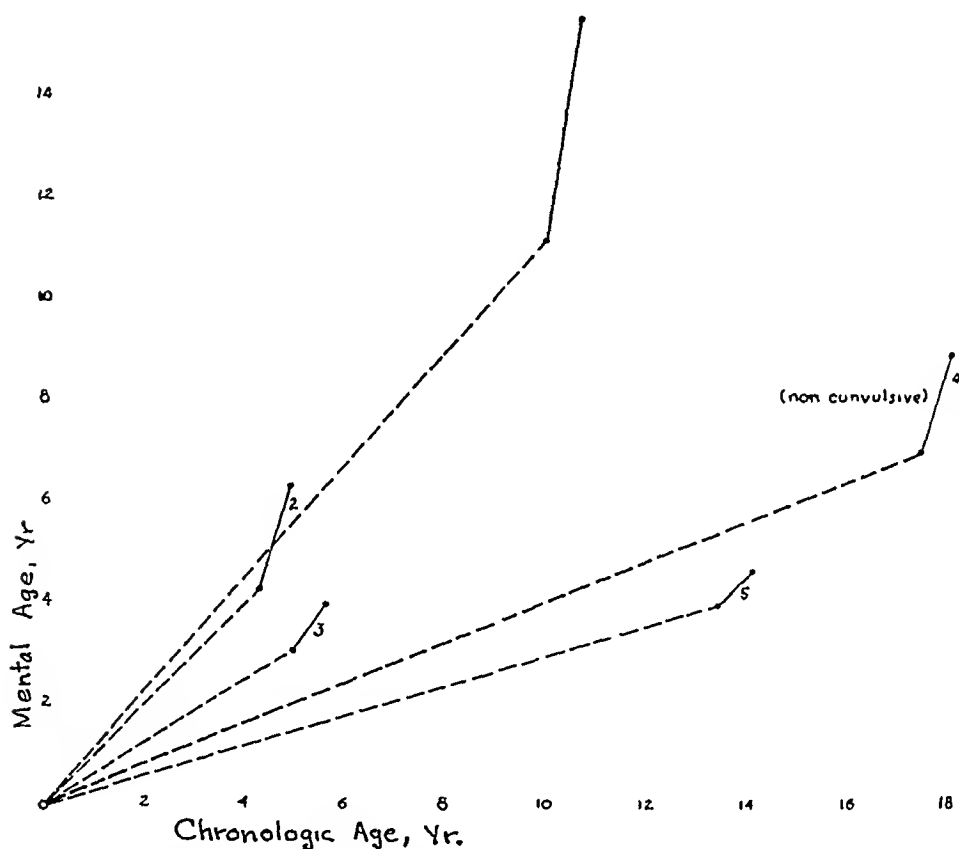


Fig 3—Relation of mental age to chronologic age, expressed in years, before and during glutamic acid therapy for 4 patients with convulsive disorders and 1 patient with a nonconvulsive disorder, as shown by performance test scores. The previous rate of development is shown by the broken line, the rate during glutamic acid therapy, by the solid line.

tioning, which not only is reflected in verbal and performance test scores but can be observed in rather basic personality changes, under the conditions of our experiment.

In cases 8 and 9 progress was much more rapid than would have been anticipated from the development prior to the glutamic acid therapy, results which are consistent with those for the rest of the experimental group.

## COMMENT

On verbal, motor and personality tests given, definite improvement following glutamic acid therapy could be observed in each of our 9 subjects during a six month interval. A number of experiments have pointed to the fact that *l* (+)-glutamic acid has a particular relation to cerebral metabolism. Weil-Malherbe<sup>18</sup> reported that *l* (+)-glutamic acid is the only amino acid known to be metabolized by slices of brain tissue. Recent investigations of Nachmansohn and his associates<sup>19</sup> suggest that the release of acetylcholine is intrinsically connected with the electrical changes during nerve activity. They found that the energy of the action potential is derived from energy-rich phosphate compounds and concluded that these compounds yield the energy for the formation of acetylcholine. As a result of these observations, they isolated an enzyme from the brain which synthesizes acetylcholine<sup>20</sup>. This enzyme, choline acetylase, becomes inactive on dialysis. Addition of *l* (+)-glutamic acid reactivates the enzyme<sup>21</sup>.

While the precise mechanism of the action of glutamic acid on the rate of acetylcholine has still to be elucidated, the intrinsic connection of an acetylcholine with nerve activity and the demonstration of an increased rate of formation of acetylcholine in the presence of glutamic acid *in vitro* make it possible to assume that the physiologic basis of the observed effects of glutamic acid is in some way related to the formation of acetylcholine. At present this seems to be the best interpretation.

## SUMMARY

The results here reported must be considered tentative because of the smallness of the group, but the consistent improvement reflected in the psychologic test scores under the conditions of our experiment suggests that glutamic acid may have a genuine facilitating effect on mental functioning in human subjects, as it does on maze learning in the white rat.

## APPENDIX

While the study is primarily objective, clinical observations in the main support the quantitative findings, and a clinical abstract of each case is accordingly appended.

18 Weil-Malherbe, H. Studies on Brain Metabolism. Mechanism of Glutamic Acid in Brain, *Biochem J* **30** 665-676, 1936.

19 Nachmansohn, D., Cox, R. T., Coates, C. W., and Machado, A. L., Action Potential and Enzyme Activity in the Electric Organ of *Electrophorus Electricus*. II. Phosphocreatine as Energy Source of the Action Potential, *J Neurophysiol* **6** 383-396, 1943.

20 Nachmansohn, D., and Machado, A. L. The Formation of Acetylcholine. A New Enzyme, "Choline Acetylase," *J Neurophysiol* **6** 397-403, 1943.

21 Nachmansohn, D., John, H. M., and Waelsch, H. Effect of Glutamic Acid on the Formation of Acetylcholine, *J Biol Chem* **150** 485-486, 1943.

CASE 1—A boy 10 years old had a history of petit mal attacks occurring on the average of one a day since the age of 2 years. The general physical and neurologic status was normal. A roentgenogram of the skull revealed nothing abnormal. The electroencephalogram showed wave and spike formations and flat-topped slow activity dominating the pattern in all leads. The petit mal attacks were completely controlled with phenobarbital, 0.06 Gm given three times a day. After a psychometric examination he was given 1 (+)-glutamic acid, 2 Gm three times a day. No change in behavior was noted. When the dose was increased to 4 Gm three times a day, the mother reported that he was very restless and overactive. His teacher reported poor conduct in school, which seemed to be due to greater distractibility. He continued to be free of seizures as long as he remained under treatment with phenobarbital and glutamic acid.

The behavior of this patient can possibly be explained on the basis of lack of need of such large doses of glutamic acid, since his intelligence quotient was high in the first place.

CASE 2—A boy 4 years old had been having attacks of petit mal for two years. There was a history of a head injury without loss of consciousness six weeks before the onset of the spells. The physical and neurologic status was normal. A roentgenogram of the skull and an electroencephalogram were normal. Treatment with diphenylhydantoin sodium and phenobarbital was ineffective. After a psychometric examination treatment with 1 (+)-glutamic acid (3 Gm daily) was substituted. The number of seizures dropped from seven or nine to one or two per day. The dose increased to 6 Gm per day, after which the mother reported that the child was much more alert and active. When the dose was gradually increased to 24 Gm per day, the child became very restless and overactive and was unable to sleep at night. A subsequent dose of 12 Gm per day maintained an optimum degree of activity and alertness. He continued to have one to two seizures per day.

CASE 3—A boy aged 5 years had been having attacks of disordered consciousness since the age of 16 months, beginning as petit mal and subsequently complicated with grand mal attacks. Several physical and neurologic examinations showed nothing abnormal. A roentgenogram of the skull revealed a disproportionately small cranial cavity, consistent with microcephaly. After a psychometric examination the boy was given 4 Gm of 1 (+)-glutamic acid three times a day in addition to 0.1 Gm of diphenylhydantoin sodium daily, which he had been receiving previously. The number of grand mal seizures was not affected, but the petit mal attacks dropped from ten or fourteen per week to four or seven per week. The mother reported that the child was much more tractable. Whereas previously he fought with the other children a great deal, he was now much more sociable and played with the other children nicely. The change in behavior began to be apparent about two weeks after the start of the glutamic acid therapy.

The father, who had not seen the child for seven weeks and was unaware of the treatment, spontaneously remarked that he appeared much brighter and more alert.

When seen in the clinic, the child showed increased motor activity. While previously he had sat quietly in his chair, he now was inquisitive and moved around frequently. Two months later the family reported considerable improvement in memory. He began to talk about the radio, which had been repaired over a year before. He also began to remember the names of people, when

taken with his mother shopping, he remembered the various groceries she bought in different stores. He also began to recognize colors. He continued this improvement throughout the six month testing period.

After a toxic reaction to an increased dose of diphenylhydantoin, treatment was changed to administration of methylethylphenylhydantoin, 0.1 Gm four times a day. This drug, in conjunction with 12 Gm of glutamic acid, controlled both types of seizures completely.

**CASE 4**—A girl aged 17 years, who appeared much younger than her chronologic age, gave a history of normal birth. She walked at 15 months, said words at 2 years and used sentences between 2 and 3 years of age. Although at one time she tended to stay by herself, she later became more friendly, but she played with younger children and was always the oldest in her group. The situation was complicated by rejection on the part of the mother, who preferred an older, normal, daughter.

In the school which she attended for one year before coming to our attention, she was doing arithmetic at the fifth grade level and was reading at the seventh grade level. On the playground she took part in all group activities but needed to be encouraged to do so. In the dormitory she was slow but did everything for herself. She was careless about her appearance and person and had to be given assistance at the time of her menstrual periods. Occasionally she wet the bed or soiled herself, but this was apparently done in retaliation against a staff member whom she did not like. Her relations with other children eventually became very poor. She pinched, slapped and pushed them without any apparent provocation. She became increasingly withdrawn, and because of this the parents were advised to remove the child and seek psychiatric advice.

When first seen, she appeared dull and withdrawn, did not hold herself erect and walked with a careless slouch. She appeared untidy in her dress and person. She was obviously resentful toward her mother, who returned the sentiment in good measure. After a psychometric examination glutamic acid medication was started. She was first given 2 Gm three times a day, and the dose was gradually increased to 4 Gm three times a day. With the latter dose she became very overactive and more antagonistic toward her mother. The older sister, who was much more impersonal in her observations than the mother, said, however, that the patient seemed to "think more about herself." The dose was reduced to 3 Gm three times a day, and she became more tractable, with evidence of more continued interest in things. When she was seen at the end of the six month experimental period, her facial expression was more alert, and her negativistic behavior was not so much in evidence, even in the presence of her mother. She stood more erect, and her exaggerated slouch had disappeared.

**CASE 5**—A boy aged 13 years had been having attacks of grand mal since the age of 4 years. He first came to our attention at the age of 2 years, when a diagnosis of serious mental retardation was made. He was premature and was born by cesarian section. A cousin had convulsions for eighteen years. The general physical and neurologic status was normal. Roentgenograms of the skull revealed no abnormality. The pneumoencephalogram showed diffuse cerebral agenesis or atrophy and localized agenesis or atrophy in the anterior parietal region, with moderate general dilatation of the ventricular system. The electroencephalographic record was disorganized, with much low to medium activity everywhere, and was interpreted as definitely abnormal. The patient had one attack every three to four months, usually rather severe and lasting from forty-

five minutes to one and one-half hours. Diphenylhydantoin sodium, 0.1 Gm twice a day, and phenobarbital, 0.03 Gm three times a day, reduced the severity of the seizures but not the frequency. After a psychometric examination the patient was given 4 Gm of *l* (+)-glutamic acid three times a day, in addition to the diphenylhydantoin and phenobarbital. About a month later his mother reported that he appeared to be more alert and attentive. The dose was then increased to 6 Gm three times a day. Two months later his mother reported he was much more alert, was no longer shy and was making a much better social adjustment. She said, "Before, the children would never play with him because he was too slow in grasping things. Now they have accepted him, and he gets along fine with them. He used to be seclusive—never wanted to go out—now he is anxious to go out and play with the other children. He enters into the games and has a good time and is not shy any more. Even the neighbors notice it."

Three months later his mother reported that in addition to the improvement already noted he "picks up the newspaper and sounds out the words, trying to read."

During the six month experimental period the seizures were not controlled, although they were less severe. If anything, the frequency was increased to two or three attacks per month. No great effort was made to control the seizures in order to see what effect the glutamic acid would have on mental ability in the presence of seizures.

**CASE 6**—A boy aged 12 years had been having grand and petit mal attacks on the average of one a day since the age of 6 years. The general physical and neurologic status was normal. A roentgenogram of the skull revealed an unusually thick calvaria and conspicuous diploic structures but no signs of increased intracranial pressure or intracerebral calcification. The electroencephalographic record was quite abnormal, without alpha activity at any time. An irregular mixture of medium voltage, slow activity was continuously seen, with frequencies varying from 3 to 6 per second. In addition, many single "slow" spikes and atypical spike and wave groups were recorded from both occipital areas. The record was considered grossly abnormal with convulsive patterns.

The grand and petit mal seizures were controlled with diphenylhydantoin sodium, 0.1 Gm twice a day, and phenobarbital, 0.03 Gm twice a day, after which the patient was given a psychometric examination and 2 Gm of *l* (+)-glutamic acid three times a day, in addition to the aforementioned medication. One month later, although the seizures were still controlled, there was no visible evidence of improved mental status. The amount of *l* (+)-glutamic acid given was then gradually increased to 8 Gm three times a day. Two weeks after the inauguration of the latter dosage the patient appeared much more alert mentally, lost his indifferent manner and was genuinely interested in what went on about him. His facial expression was no longer dull, and he smiled appropriately.

One month later his mother said, "He used to get lost when I sent him on an errand and couldn't find the house. Now he finds it easily." She also reported, "He used to be very poor at riding a bicycle. Now he is very good. He used to be awkward and clumsy in handling eating utensils, such as a knife and fork, as though he didn't quite know how to use them. Now he handles them all right." She said further, "He used to be a little uncertain in his gait. Now I don't notice it any more. Then, too, he used to stutter a lot and fumble for words. This has disappeared. He was also 'hard-headed' and stubborn. Now he is much more

tractable He hasn't been to school for three years and was in the fourth grade Now they took him back to school and put him in 6 A He certainly isn't nervous any more and 'catches on' a lot quicker"

CASE 7—A girl aged 16 years had been having grand mal attacks since the age of 12 years, the seizures occurring on the average of once a month and lasting a few minutes The general physical condition was normal Neurologic examination revealed nothing abnormal except for congenital nystagmus A roentgenogram of the skull was normal Three electroencephalograms were taken at the ages of 12, 14 and 16 years, respectively The patterns of all three were interpreted as consistent with a convulsive disorder, with a suggestion of a focus in the occipital area in the first two and a focus in the right parieto-occipital region in the third A pneumoencephalogram was also normal The patient had for three years been under treatment with diphenylhydantoin sodium, 0.1 Gm three times a day, and phenobarbital, 0.03 Gm three times a day, and had been free of seizures After a psychometric examination she was placed under a regimen of 1 (+)-glutamic acid, 2 Gm three times a day One month later no change was noted She still presented her characteristic picture of listlessness and indifference, with a certain constant querulous way of discussing her problems From her facial expression she appeared apathetic and slightly anxious The dose of glutamic acid was then increased to 4 Gm three times a day, and when she was seen about five weeks later she was smiling and vivacious Whereas previously she had complained about her teachers and her inability to get good grades, she now said she was getting good marks and was no longer bothered by the teacher, though she still thought she was a "pill" In later months she regained a normal interest in social activities and talked about her "dates," dancing and so forth She has maintained this improvement to date with the same medication

CASE 8—A girl 2 years of age had a history of retarded development, first noted about the age of 6 months Instrumentation was necessary at birth She had her first teeth at 6 months of age and seemed unusually quiet At 7 months she did not reach for things and did not try to sit up She sat up at 15 months, but at 2 years of age she made no effort to walk or talk She was bottle fed from birth, and at 23 months of age she was unable to hold her bottle The family history was noncontributory Physical examination showed defective musculature, with no evidence of abnormal control of muscular movements The condition was believed to be that of a developmental defect of the muscular system, with defective cerebral development as well Roentgenograms of the skull and spine revealed nothing abnormal Chronaxia showed no evidence of disease or defect of the lower motor neurons

After a psychologic examination the child was given glutamic acid, 2 Gm three times a day One month later the parents reported that the child was more alert and attempted to gain their attention She was able to pile blocks one on the other, a performance of which she had not been capable before Medication was then discontinued for a month because of a gastric disturbance, and the child lost interest in her blocks and was unable to pile them up The medication was then started again, with a dose of 1 Gm of glutamic acid three times a day, and the dosage was gradually increased until she was able to tolerate 4 Gm three times a day In the next two months she learned to pile up her blocks again and began to notice things When seen just before the end of the six month experimental period, she had a bright expression and showed motor overactivity She was able to pull herself up to a standing position and could walk with assistance



The attention span had increased considerably. She reached for things, and when they were just out of her reach she persisted in trying to get them. The parents also reported she said the words "da-da" after them.

CASE 9—A boy 16 months of age had had a normal birth. The mother noticed that the baby, although gaining weight normally, never smiled, followed objects with his eyes or held objects in his hands. His head also appeared slightly larger than that of other infants. At the age of 6 months he began to have attacks characterized by flexion, stiffness and slight trembling of all four extremities. These attacks lasted about two minutes and were followed by sleep for a half-hour or more. They recurred from ten to fourteen times a day at first but later subsided to an average of one a day. The patient was never able to sit up, roll around in bed or stand up. Gain in weight and stature was apparently normal. Physical examination revealed slight enlargement of the head, which was thought to represent abortive hydrocephalus. The rest of the neurologic examination revealed no abnormalities. Roentgenograms of the skull and spine were normal. The seizures were controlled during the stay in the hospital with 0.03 Gm of phenobarbital daily.

After a psychometric examination, glutamic acid therapy was started, the dose gradually being increased to 2.5 Gm three times a day. Four weeks later the child was observed to be more active, turning over and getting up on his knees. Two months later he sat up without support, walked when held, was more playful and noticed things more. At the end of the six month experimental period he maintained his steady improvement and was walking alone.

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## NEUROLOGIC MECHANISM FOR CERTAIN PHENOMENA IN TETANY

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THIS PAPER is first and foremost a contribution to the elucidation of the neurologic mechanism for the Trousseau and von Bonsdorff phenomena, with special regard to the changes in excitability of the nerve during and after ischemia. In the second place, it is intended to throw further light on the mechanism for the spontaneously occurring symptoms of tetany.

The Trousseau phenomenon signifies here the tetanic spasm following pneumatic compression of the arm, while the von Bonsdorff phenomenon means the facilitation of tetanic spasm induced by hyperventilation after preceding compression of the arm. Closer analysis shows, however, that not only the spasm but also the sensory symptoms of irritation of the typical spontaneous attack of tetany are obtained when these phenomena are precipitated. The spontaneous attack of tetany is, in fact, reproduced in detail. One may therefore expect to be able to find a single explanation of all three phenomena. It seems desirable, therefore, to give first a brief survey of the spontaneous symptoms of tetany.

As is well known, the various symptoms of irritation in an attack of tetany manifest themselves in the following sequence. First of all, tingling sets in around the mouth and, peripherally, in the extremities. The tingling then increases in intensity, while it spreads proximally up over the extremities and over the face. Somewhat later a sensation of tension or spasm appears in the muscles of the mouth, the hands and the lower portion of the legs. This sensation of spasm increases in intensity and spreads in the same way as the tingling. Somewhat later a tonic spasm sets in, commencing in the muscles in which the sensation of spasm first occurred. If the attack is aggravated, the spasms spread proximally up over the extremities to the trunk. Fasciculation in the muscles, verging on spasm, is common, though but little noticeable in man. Spasm in the laryngeal muscles may set in at an early stage, as may also epileptic fits. The last-mentioned symptom, however, lies beyond the scope of this paper. As first shown by Grant and Gold-

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man,<sup>1</sup> active tetany can easily be induced experimentally by forced respiration

The mechanism which produces these peculiar and spectacular symptoms has long been obscure. The results of the earlier experimental investigations on animals concerned with spasm and fascicular twitches are conflicting (Mustard<sup>2</sup>, Carlson and Jacobson<sup>3</sup>, Paton, Findlay and Watson<sup>4</sup>, Luckhardt, Sherman and Serbin<sup>5</sup>, Spiegel and Nishikawa<sup>6</sup>) and need not be summarized here. All the observations seem to show that the spasm is dependent for its full development on the integrity of tracts high up in the central nervous system.

Observations and deductions differing from those of the authors just referred to were made by West<sup>7</sup> in an extensive study on parathyroidectomized dogs. He classified the motor manifestations of parathyroid tetany in dogs as tonic, clonic and fibrillary. By "fibrillary" he meant repeated rapid contractions of small groups of muscle fibers. Since then Denny-Brown and Pennybacker<sup>8</sup> have defined fibrillation as contractions of individual muscular fibers, whereas West's term seems to correspond most closely to what is now called "fasciculation."

West found that all motor elements remained intact in the hindlegs if the spinal cord was transected in the dorsal or the cervical region. "Fibrillary" tetany, or fasciculation, was retained after section of the peripheral nerve, tonic tetany was not. Tonic tetany likewise ceased after deafferentiation by transection of the dorsal roots and was thus dependent on the integrity of the lowest spinal reflex arc. From these observations he drew the conclusion that parathyroid tetany arises essentially from the action of a circulatory factor peripherally on some site in the muscle to cause contractions of individual muscle fibers. Owing to

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1 Grant, S. B., and Goldman, A. A Study of Forced Respiration. Experimental Production of Tetany, *Am J Physiol* **52** 209, 1920.

2 Mustard, H. J. A Study of Certain Tonic and Reflex Nervous Impulses as Factors in Parathyroid Tetany, *Am J Physiol* **29** 311, 1912.

3 Carlson, A. J., and Jacobson, C. Further Studies on the Nature of Parathyroid Tetany, *Am J Physiol* **28** 133, 1911.

4 Paton, D. N., Findlay, L., and Watson, A. Tetania Parathyreopriva. The Parts of the Central Nervous System Involved, *Quart J Exper Physiol* **10** 233, 1916.

5 Luckhardt, A. B., Sherman, M., and Serbin, W. B. On the Origin of the Muscular Tremors, Clonic and Tonic Spasms in Parathyroid Tetany, *Am J Physiol* **51** 187, 1920.

6 Spiegel, E. A., and Nishikawa, Y. Der zentrale Mechanismus der Tetaniekrämpfe und ihre Beziehungen zur Enthirnungsstarre, *Archiv f. d. Neurol. Inst. u. d. Wien Univ* **24** 221, 1923.

7 West, R. Studies in Neurological Mechanism of Parathyroid Tetany, *Brain* **58** 1, 1935.

8 Denny-Brown, D., and Pennybacker, J. B. Fibrillation and Fasciculation in Voluntary Muscle, *Brain* **61** 311, 1938.

an interplay of nerve impulses requiring an intact spinal reflex, the essential, or "fibrillary," tetany is converted into its tonic form

In experiments on frogs and cats, Kuffler<sup>9</sup> recently studied the motor symptoms of tetany, which in these animals, according to him, are dominated by true fibrillation, as distinct from fasciculation, which he held to be due to impulses originating in the region of the end plates. He asserted it was probable that the motor symptoms of tetany were caused by impulses arising in synapses and end plates.

True fibrillation presumably occurs also in man, though it has not yet been observed or investigated. By means of electromyography, however, it should easily be shown if present. But the dominant sensory and motor phenomena of irritation associated with tetany, in man, as previously outlined, are primarily due to the effect of changes in the blood not on the muscle or the synapses but on the nerve itself, as I have shown<sup>10</sup> with the following, simple technic.

If a pneumatic cuff is inflated over the area of observation of the systolic pressure, just proximal to the elbow of the one arm, the muscles of the hand and about 40 cm of the peripheral stretch of their nerve supply are excluded from the circulation and from the effect of changes in the blood. Nevertheless, on hyperventilation tingling, a feeling of tension and spasm set in with equal rapidity and with almost the same intensity in the two arms. Thus, in this case the muscle, the nerve endings and the peripheral part of the nerve can scarcely play any part in the production of the symptoms.

But if the cuff is moved higher and higher up the arm, the conditions will be crucially changed. It will be found increasingly difficult to induce symptoms of irritation in the ischemic arm. If the cuff is placed as high as possible, a spasm that cannot be controlled by volition will develop in the opposite arm before it can be produced in the ischemic one. Although all the symptoms of irritation can eventually be produced in the ischemic arm, they are throughout of far less intensity there. This can scarcely be interpreted otherwise than on the assumption that the impulses which give rise to the symptoms set out from, and can be most easily induced in, the proximal part of the peripheral stretch of nerve. Furthermore, the nerve fibers which first give rise to the impulses must be the longest ones in the extremities, since the symptoms begin at the periphery and spread centripetally.

9 Kuffler, S. W. Excitability Changes at Neuro-Muscular Junction During Tetany, *J. Physiol.* **103** 403, 1945.

10 Kugelberg, E. (a) Accommodations och rheobasbestämningar i människans motoriska och sensibla nerver. *Nord med.* **19** 1343, 1943, (b) Accommodation in Human Nerves and Its Significance for the Symptoms in Circulatory Disturbances and Tetany, *Acta physiol. Scandinau.* 1944 suppl. 24.

Thus, in tetany the nerve is not affected uniformly along its entire course. This is indicated also by the fact that the electrical excitability was found to be increased to a much higher degree proximally than distally both in subjects with parathyroprivic tetany and in those with tetany due to hyperventilation. The fall of the rheobase and the poorer accommodation were more pronounced proximally. Moreover, it was found that when fasciculation occurred in a muscle whose motor nerve fibers were being tested electrically the accommodation was almost nil proximally while the rheobase was very low, an observation which indicates that spontaneous discharges were occurring in the tested region. A low rheobase and poor accommodation are the electrically measurable equivalents of "increased excitability."

The typical form of tingling associated with tetany was found to arise in fibers transmitting light touch. As shown by the above mentioned observations, the fasciculations originate in the motor fibers. Finally, the sensation of spasm is not caused, as might have been expected, by the muscular contraction.

If a pneumatic cuff is distended above the elbow on the one arm and the experimental subject begins to hyperventilate, it will be found after a while that spasms occur in both hands, with an intense feeling of cramp (Kugelberg<sup>10b</sup>). When the cuff has been kept on for twenty to thirty minutes, the motor fibers are paralyzed as a result of the ischemia, as are the tactile fibers and the fibers of muscle sense. Although the hand is limp and the sensation of touch, pressure and position have vanished, a peculiar, "fantom limb" sensation remains. It feels as though the hand were assuming the typical spastic posture and as though the muscles were equally contracted in the two hands. Thus the sensation of spasm cannot be produced at the periphery by the actual contraction, but is a paresthesia that originates in a discharge from the proximal part of afferent fibers, presumably the muscle afferent fibers.

The spasm is caused either by impulses from the hyperexcitable discharging motor fibers or, reflexly, by impulses from the afferent fibers in the same region of the nerve. The latter alternative would harmonize with West's observation on dogs that spasm is dependent on the integrity of the lowest reflex spinal arc. It would be permissible to generalize from the experiments on dogs with reference to man if the statement by Flick and Hansen<sup>11</sup> is correct that the spasm in the Trousseau phenomenon cannot be produced if the nerves are blocked proximal to the cuff, an observation which would show that the spasm is really a reflex. However, experiments now proceeding indicate that the

11 Flick, K, and Hansen, K. Zur Elektrophysiologie sogenannter tonischer Verkürzungszustände quergestreifter Skelettmuskeln. Das Trousseau'sche Phänomen und die Pfotenstellung bei der Atmungstetanie, *Ztschr. f. Biol.* 82: 387, 1925.

Trousseau spasm is not a mere reflex, hence the question whether the spontaneous tetanic spasm is a reflex or not must be left open for the present

Thus, provided that the aforementioned observations are correct, the mechanism for the origin of the symptoms dealt with here may thus be summed up as follows. The changes in the blood increase the excitability of the nerve, i. e., lower the rheobase and abolish the accommodation. This gives rise to spontaneous discharges primarily in the proximal part of the longest nerve fibers, from which the focus spreads, with increasing aggravation of the symptoms. The spontaneous activity starts in the tactile fibers, from which the typical sensation of tingling originates, and somewhat later is set up in other afferent fibers, which produce the feeling of tension. About the same time it reaches also the motor fibers, giving rise to fasciculations. The spasm is caused either by the activity in the motor fibers or, reflexly, by the activity in the afferent fibers.

#### THE TROUSSEAU PHENOMENON

Where the impulses that give rise to the spasm in the Trousseau phenomenon originate is a question which has been much discussed (for a review of the literature see Nothman<sup>12</sup> and Lewis<sup>13</sup>). Recently, however, Lewis<sup>13</sup> and, independently, I<sup>10</sup> have shown that these impulses are produced by the effect of ischemia on, mainly, the proximal part of the nerves.

**CASE 1**—V. O., a woman aged 36, who was suffering from parathyroid tetany following a strumectomy in 1933, was treated at the clinic. She had not received any effective treatment before her admission, on April 17, 1945, when she had fascicular twitches and a feeling of tension in the small muscles of the hand, as well as occasional tactile paresthesia in the fingers. The amount of calcium in the blood serum was then 5.2 mg per hundred cubic centimeters. She was treated with dihydrotachysterol and improved rapidly. But when the treatment was suspended for a fortnight, she had a relapse. She was then placed definitely under treatment with a suitable dosage. The amount of calcium in the serum, as well as the excitability of the nerves, gradually underwent marked changes, and, concomitantly, the Trousseau phenomenon could be elicited with comparative ease. Good facilities for studying the phenomenon were thus afforded.

**Symptoms**—It was at first found that when the Trousseau phenomenon was precipitated all the sensory and motor phenomena in the spontaneous attack of tetany were reproduced, and in exactly the same way as regards sequence and spread.

The first symptom was tingling in the finger tips, spreading centripetally toward the place of compression. A few tenths of a second after the tingling had set in the feeling of tension in the muscles of the hand began, and at about the same time, but usually somewhat prior to its appearance, fasciculation started.

<sup>12</sup> Nothman, M. Tetanie, in Bumke, O., and Foerster, O. *Handbuch der Neurologie*, Berlin, Julius Springer, 1937, vol. 15, p. 173.

<sup>13</sup> Lewis, T. Trousseau's Phenomenon in Tetany, *Clin. Sc.* 4: 361, 1942.

in the same muscles. The feeling of tension increased and spasm began in the muscles of the hand. When the spasm had been well established, the fascicular twitches could no longer be observed. The feeling of tension and the spasm then spread, possibly up to the muscles of the forearm. The culmination of the intensity and spread of all the symptoms of irritability was reached in two to four minutes. The intensity then diminished, and the area of distribution decreased in reverse order of that of involvement. After seven to nine minutes all the symptoms of irritation ceased, likewise in reverse order of that of their occurrence.

When, at the time of the patient's admission to the clinic, the various symptoms of irritation were most pronounced, they set in, with intervals of a few seconds, after about ten seconds' compression of the upper portion of the arm. The first motor symptom was fasciculation in the muscles of the hand, so intense that it looked as though their surfaces were seething, it was rapidly followed by tonic spasms in these muscles. The thumb was first adducted, and this was immediately followed by flexion of the fingers at the basal joints and extension at the other joints. The muscular contractions were so strong that the patient could not execute any voluntary movements of the fingers and wrist. The tingling spread up to the cuff, which was applied to the middle of the upper portion of the arm. The cuff had to be removed after the lapse of a few minutes, owing to intense pain in the contracted, ischemic muscles.

As the patient's condition improved, the symptoms of irritation diminished in intensity, and their range of distribution decreased. They set in somewhat later than before, viz., after the lapse of one to one and a half minutes, and wore off sooner. The last motor symptom that remained was fasciculation in the muscles of the hand. At the same time, the tactile paresthesia was felt up to the knuckles. In the next stage the tactile paresthesia was the only remaining symptom of irritation. After additional administrations of dihydrotachysterol, the tingling also finally vanished.

The table shows the course of the process in relation to the blood calcium and the rheobase, as well as the accommodation in the ulnar nerve, which was stimulated proximal to the elbow, with a minimal twitch in the first dorsal interosseus muscle as an index. The place of stimulation on the nerve was the point of the lowest threshold, which was carefully determined, whereupon the spot was marked. The electrode was fixed with some strips of plaster (for technic, see Kugelbeig<sup>10b</sup>). In all subsequent determinations, the electrode was then placed on the same mark, care being taken that the experimental subject always kept the arm in the same position, with a view to comparable values.

It should be pointed out that not only the spasm but also all the symptoms of irritation dealt with here arose in the proximal part of the ischemic nerve. This was ascertained with the same technic as that adopted for study of the spasm and tingling. Thus, the fasciculation associated with the Trousseau phenomenon is not caused by irritation of the muscle or the nerve endings but is produced by irritation of the nerve itself.

*Changes in the Rheobase of the Nerve During Ischemia and Its Relation to the Phenomena of Irritation*—When the muscle is contracted

during the tonic stage, the threshold of excitation cannot be determined. This limitation, however, is of no consequence, as the threshold can be correlated with the fasciculation which precedes the spasm. Moreover, unduly high values for the rheobase are obtained when intense fasciculation is proceeding in the muscle. In fact, the minimal twitch, adopted as an index, cannot be observed in the midst of the general activity, hence, a more marked twitch with a somewhat higher threshold must be taken instead as an index.

The cuff was placed as high up on the arm as possible, in order to avoid affecting the position of the electrode at the elbow and changing the rheobase. Since fasciculation, as well as all the other symptoms of irritation, sets in more rapidly the farther proximally the cuff is placed, the changes in the rheobase as measured at the elbow cannot be directly correlated with the time of manifestation of the fasciculations, which in this case set in much farther proximally. The changes in

*Tabulation of Data for V O on Different Dates*

Date (1935)	Blood Calcium, Mg /100 Cc	Rheobase, ma	Accommodation Slope *	Spontaneous Symptoms of Irritation	Fully Developed Symptoms of Irritation on Compression 15 Cm Proximal to Elbow
4/17	5.2	0.35	About 0	Tingling and fasciculation in hands	Tingling and intense spasm up to site of compression
4/20		0.9	17	None	Tingling up to wrist, slight spasm in hand muscle
4/24	8.2	1.8	18	None	None
4/27		1.6	17	None	Tingling in finger tips
5/ 2	7.0	1.2	18	None	Tingling up to knuckles, fasciculation and tension in hand muscles

\* By the term "accommodation slope" is meant the slope of the straight portion of the curve showing the relation of the number of rheobases necessary for a threshold muscular contraction to the duration of the slowly rising current stimulating the nerve of the contracting muscle (Kugelberg <sup>10b</sup>).

threshold were correlated, instead, with the time of incipience and cessation of fasciculation in the other arm, where they had been elicited by compression above the elbow at a level corresponding to the position of the stimulating electrode. The results of three determinations of the rheobase during ischemia, made on different days with differing amounts of blood calcium and initial values of the rheobase, as well as varying intensities of the symptoms of irritation during ischemia (table), are shown in chart 1.

It will be seen from the chart that the electrical excitability measured in terms of the rheobase, rapidly increases after ischemia (the rheobase decreases) for some tenths of a second, as has previously been observed in association with oxygen deficiency in nerves *in vitro* by Thorner,<sup>11</sup>

<sup>11</sup> Thorner W. Ueber das Erregungsstadium der Erstickung und Narkose. *Arch f d ges Physiol* 204:747, 1924.



Heinbecker,<sup>15</sup> Lehmann<sup>16</sup> and others and as observed with ischemia in situ in experimental animals by MacCallum,<sup>17</sup> Paton and associates<sup>4</sup> and Morris,<sup>18</sup> and in man by Kugelberg<sup>10</sup>, and, with respect to sensory fibers, by Thompson and Kimball<sup>19</sup>

The excitability reaches its maximum after the lapse of about three minutes and then diminishes to pass the initial value, in this case after ten to twelve minutes. The absolute value reached by the increase in excitability is evidently determined by the initial value of the rheobase, which, in turn, as generally supposed, is determined by the amount of ionized calcium. The lower the rheobase in a given case, the lower

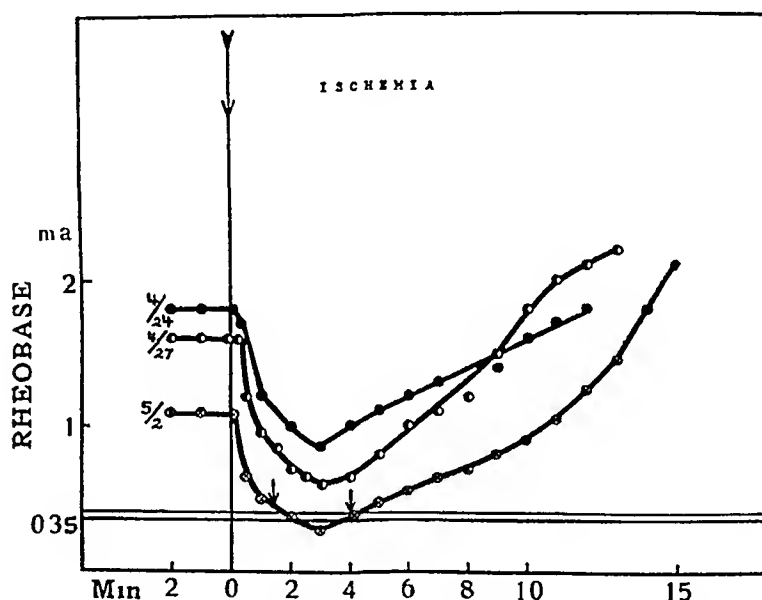


Chart 1—Threshold curves during ischemia obtained from the ulnar nerve on stimulation at the elbow, with a minimal observed twitch in the first dorsal interosseus muscle as an index. The patient (V O) was tested on different days with different values for the blood calcium and the rheobase and with various symptoms of irritation caused by ischemia (table)

The double horizontal line indicates the threshold when spontaneous activity arises in the tested nerve fibers by diminution of the blood calcium. The arrows indicate the time when the spontaneous activity due to ischemia begins and ceases at the tested point

15 Heinbecker, P. Effect of Anoxemia, Carbon Dioxide and Lactic Acid on Electrical Phenomena of Myelinated Fibers of the Peripheral Nervous System, *Am J Physiol* **89** 58, 1929

16 Lehmann, J. E. The Effect of Asphyxia on Mammalian A Nerve Fibers, *Am J Physiol* **119** 111, 1937

17 MacCallum, W. G. Ueber die Uebererregbarkeit der Nerven bei Tetanie, *Mitt a d Grenzgeb d Med u Chir* **25** 941, 1913

18 Morris, N. Anoxemia and the Increased Electrical Excitability of the Neuromyone, *Brit J Exper Path* **3** 101, 1922

19 Thompson, M., and Kimball, S. Effect of Local Ischemia upon Human Nerve Fibers in Vivo, *Proc Soc Exper Biol & Med* **34** 601, 1936

will be the level to which it falls, or, in other words, the less the amount of ionized calcium, the higher will be the increase in excitability

If the changes in threshold are correlated with the general symptoms of irritability, it is evident that these symptoms will manifest themselves precisely during the period of increased excitability. They appeared, as before stated, after the lapse of ten seconds to one and a half minutes and wore off three to nine minutes later. They reached their culmination approximately in from two to four minutes, a period which corresponds to the maximum for the increase of excitability, and, like the latter, their intensity was determined by the original value for the rheobase and the ionized calcium. The correlation, however, will be still more exact if only the motor threshold is correlated with the fasciculation.

Fasciculations manifested themselves spontaneously at a blood calcium level of 5.2 mg per hundred cubic centimeters and a rheobase of 0.35 milliampere. As accommodation at the same time was absent, there are good reasons for assuming that the fasciculations had appeared also at the point of determination. When the rheobase rose to 0.4 milliampere, they vanished. During ischemia, on the other hand, fasciculations likewise did not manifest themselves until the rheobase had fallen to 0.42 milliampere, and they ceased at approximately the same value, 0.38 milliampere (test on May 2, chart 1). From this it may be inferred that when the increase in excitability reaches a certain crucial value at a given point, spontaneous activity will manifest itself in the nerve fiber. This value can be attained by a diminution in the amount of ionized calcium, as in the spontaneous attack of tetany, or by ischemia. The intensity of the spontaneous activity during ischemia is determined by the amount of calcium in the blood. (A similar effect was described by Lehmann<sup>16</sup> on cat nerve in vitro during asphyxia.) At high values for the blood calcium in man no activity at all occurs. Normally, it occurs in the longest tactile fibers. On diminution of the blood calcium, activity develops in other afferent fibers, the motor fibers and the shorter tactile fibers, giving rise to a sensation of tension, the Trousseau phenomenon, fasciculations of varying intensity and the spread of tactile paresthesia.

#### VON BONSDORFF PHENOMENON

Von Bonsdorff<sup>20</sup> described a symptom for the diagnosis of latent tetany. He inflated a pneumatic cuff over the area of determination of the systolic pressure on the upper portion of the arm and kept it on for ten minutes. It was then removed, and the patient was told to hyperventilate. In the previously ischemic arm the typical tetanic spasm was then produced earlier than in the other arm—in cases of latent tetany even

<sup>20</sup> von Bonsdorff, B. Några fall av tetani bland varnplikliga, Finska läk-sällsk. handl. 72: 108, 1930.

after a few minutes or after a few deep breaths. In certain cases the phenomenon could be rapidly induced even when the Chvostek, Trousseau and Erb phenomena could not be elicited, and he found it to be a valuable supplementary sign in the diagnosis of tetany.

CASES 2 and 3—Two patients suffering from tetany were treated at the clinic. K. D., a man, and B. S., a woman, had been admitted because of attacks of tetany which had been produced mainly by hyperventilation. In the case of K. D. they had commenced in connection with trumpet blowing. Both the patients showed a slightly positive Chvostek phenomenon but negative Trousseau and Erb phenomena and normal values for the blood calcium. On hyperventilation, the typical spastic posture of the hands manifested itself after the lapse of two to five minutes, being equally pronounced on the two sides. Thus, though these patients normally had no definite signs of imbalance of the calcium ions, which determines the excitability of the nerve (the alkali reserve, however, was not determined), symptoms of active tetany had manifested themselves with abnormal rapidity on hyperventilation. This experience, which had brought them to the hospital, shows the usefulness of hyperventilation tests in diagnosis in certain cases. Since the typical tetanic spasm had been rapidly induced on hyperventilation in both patients, they offered particularly good facilities for an analysis of the von Bonsdorff phenomenon.

*Analysis of the Phenomenon*—Place of Precipitation. With compression of the pneumatic cuff over the area of determination of the systolic pressure, the whole arm (muscle, nerve endings and nerves) peripheral thereto is exposed to ischemia. In the phase of recovery from ischemia, changes in some of these tissues which tend to facilitate precipitation of the attack of tetany on hyperventilation evidently occur. In order to ascertain where the critical change originates, the experiment described in the following protocol was made.

Subject K. D.

Preliminary test (Oct. 12, 1944). Hyperventilation. After four minutes spasms in both hands and in the region of the facial nerve on both sides set in simultaneously and with the same intensity.

Experiment A. A pneumatic cuff was distended to 200 mm. high up on the upper portion of the left arm.

Five minutes. A new cuff was placed around the lower part of the upper portion of the same arm and distended, and the upper cuff was removed. Hyperventilation was begun.

Six minutes. Spasm appeared in the left hand and in a few seconds could not be voluntarily controlled.

Nine minutes. Intense spasm continued in the left hand. Spasm appeared in the face. Paresthesia began in the right hand. Hyperventilation was discontinued.

Experiment B (Oct. 13, 1944). A pneumatic cuff was distended over the area of determination of the systolic pressure, just proximal to the elbow of the right arm.

Five minutes. The cuff was removed, and a new one was placed immediately above and distended, so that its lower edge lay on the site of the upper edge of the first cuff. Hyperventilation was begun.

Eight minutes Spasm appeared in the left hand

Thirteen minutes Spasm continued in the left hand, none occurred in the right hand Hyperventilation was discontinued

Experiment A shows that for full development of the phenomenon it suffices if the hyperventilated blood is brought into contact with the proximal part of the previously ischemic nerve. If the flow of blood is blocked proximal thereto, the phenomenon, as is to be expected, does not appear (experiment B)

That the impulses which give rise to the phenomenon come mainly from the proximal part of the previously ischemic stretch of nerve can be shown in the following way. A pneumatic cuff is placed on each arm and distended and is kept on for five minutes. A new cuff is then distended around the upper part of one forearm, and the first cuffs are removed. When the experimental subject then begins to hyperventilate, the spasm sets in with about the same rapidity and intensity in the two hands. This shows that muscles, nerve endings and the peripheral stretch of nerve do not play any appreciable part in the precipitation of the phenomenon.

*Optimal Place of Precipitation in the Arm*—Since sensitivity of the nerve to ischemia increases from the peripheral to the proximal part (Lewis, Pickering and Rothschild<sup>21</sup>) and since this applies also to the effect of those changes in the blood which give rise to tetany (see introductory section), it may a priori be expected that the von Bonsdorff phenomenon could be more readily precipitated the more proximally on the arm the cuff has been placed. This, in fact, proved to be the case. If the cuffs are placed at different levels on the arms and if they are kept on for the same length of time, it will be found on hyperventilation that the spasm will set in earliest and with greatest intensity on the arm on which the cuff has been placed more proximally. The phenomenon, however, can be precipitated also on the forearm, but it will be less pronounced and may require a longer preceding compression.

*The Time Factor and Its Relation to Electric Excitability in the Nerve*—I further investigated how long after the removal of the pneumatic cuff the spasm is most readily induced in the previously ischemic arm. It was found, somewhat to my surprise, that if hyperventilation was deferred for ten to fifteen minutes after the removal of the cuff the appearance of the spasm was actually impeded if the cuff had been placed on the proximal part of the upper portion of the arm. This is illustrated by the following protocol

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<sup>21</sup> Lewis, T. Pickering, G. W. and Rothschild, P. Centripetal Paralysis Arising Out of Arrested Bloodflow to the Limb Including Notes on a Form of Tingling, *Heart* 16:1 1931

Subject B D

Preliminary test Nov 20, 1944 Hyperventilation The spasm set in simultaneously and with the same intensity in the hands in five minutes

Experiment A pneumatic cuff was placed as far proximally as possible on the right arm and was distended to 200 mm

Ten minutes The cuff was removed

Twenty-five minutes Hyperventilation was begun

Thirty-two minutes Spasm appeared in the left hand and could not be voluntarily mastered, no spasm occurred in the right hand

Thirty-six minutes Spasm continued in the left hand, but none appeared in the right Hyperventilation was discontinued

Forty-five minutes Spasm ceased in the left arm

These general relations were confirmed in several experiments In chart 2 the change from increased to decreased sensitivity to hyper-

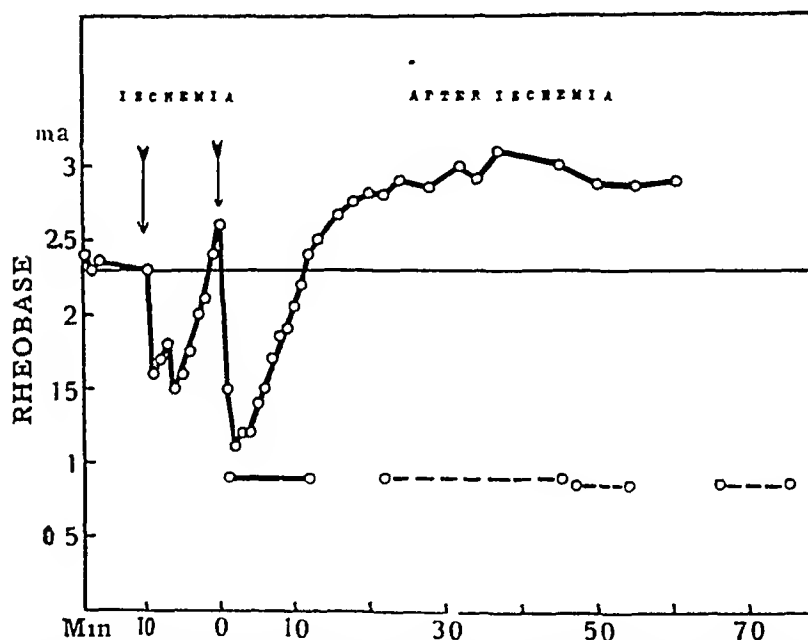


Chart 2—Threshold curve obtained from the ulnar nerve after ischemia, showing relation to facilitation and inhibition of spasm induced by hyperventilation in the previously compressed arm

The horizontal lines below the curve may be interpreted as follows. The solid line in the circles indicates duration of facilitation of spasm, the broken line with circles, the duration of inhibition of spasm

ventilated blood is strikingly illustrated by the curve for the changes in the rheobase after ischemia

The rheobase was determined on fibers to the first dorsal interosseus muscle in the ulnar nerve, which had been stimulated at the elbow. The determination was made on experimental subject B S before and after ten minutes of ischemia. Afterward, the test for the von Bonsdorff phenomenon was made, the subject beginning the hyperventilation at various intervals after the removal of the cuff. On each occasion the

hyperventilation was arranged in such a way that the spasm continued for about ten minutes. As shown in chart 2, the excitability of the motor nerve fibers was considerably enhanced on the removal of the cuff. This applies not only to the rheobase but also to the accommodation, which fell toward zero. At the same time the excitability in the sensory nerve fibers was doubtless likewise intensified, since spontaneous activity was set up in them causing the "pins and needles" paresthesia and the so-called pseudospasm (Lewis and associates<sup>21</sup>). After about ten to twelve minutes this increase in excitability was converted into a decrease, which probably continued for hours.

If, as shown in chart 2, the hyperventilated blood was brought into contact with the proximal part of the previously ischemic nerve during the stage of increased excitability, the von Bonsdorff phenomenon was induced. If, instead, the changed blood was brought into contact with the nerve during the stage in which the excitability was diminishing, the occurrence of all the symptoms of tetany was retarded. The von Bonsdorff phenomenon is evidently precipitated by a summation of the postischemic increase of the excitability in the nerve and that induced by hyperventilation, with resulting spontaneous activity, which gives rise to symptoms of irritability.

#### COMMENT

In the first few minutes during and after ischemia an increase of excitability exists in the nerve. The same effect is produced by the changes in the blood which give rise to tetany. When the excitability reaches a crucial value, the nerve begins to discharge spontaneously. The activity starts in the proximal part of the longest tactile fibers and then proceeds to somewhat shorter ones. When the resulting paresthesia has reached approximately the wrist or the middle of the forearm, the activity starts in the longest motor fibers and in other afferent fibers, presumably to muscle, and then passes to increasingly shorter fibers. This strict sequence in the appearance of spontaneous activity can scarcely be correlated in detail with any known physiologic or anatomic characters in the nerve itself.

Certain facts indicate that this phenomenon can be correlated with the thickness of the fibers. Evidently, it is connected with the large fibers. Moreover, the longest fibers transmitting light touch must be presumed to be thicker than the longest motor fibers, since, as shown in the ulnar nerve in man (Kugelberg<sup>10</sup>) they have a considerably lower rheobase. In order to fit in with this hypothesis, the muscle afferent fibers should have a thickness corresponding to that of the motor fibers, but for man no data are available on this matter.

The greater tendency to activity in the proximal portion of the nerve may be due to the fact that the individual nerve fibers taper toward

the periphery, owing to the branching of the fibers (Eccles and Sherrington<sup>22</sup>, Bjorkman and Wohlfart<sup>23</sup> and others) Certain data indicate also that, as first stated by Schwalbe,<sup>24</sup> the longest fibers are thicker than the shorter ones It remains to be shown that the longest and thickest motor fibers and muscle afferent fibers are thicker than the short tactile fibers However, there are evidently so many gaps in the chain of evidence that it would be unwise at present to press the theory too far

It should also be noted that localization of the spontaneous activity can be correlated with the tendency to respond with iterative discharges to a constant electric current Thus, the threshold for prolonged iterative discharges is lower in tactile than in motor fibers and lower in long than in short motor fibers (Kugelberg<sup>10</sup>), as well as lower in the proximal than the distal portion of a motor nerve (Kugelberg and Skoglund<sup>25</sup>)

#### SUMMARY

The observations on the Trousseau and on the Bonsdoiff phenomenon may be summarized as follows

1 In the Trousseau phenomenon, all the symptoms of irritation in spontaneous attack of tetany are produced in identically the same way with regard to sequence and distribution Tactile paresthesia, fasciculation, the sensation of spasm and the spasm itself appear in the order of enumeration They begin peripherally and spread centripetally

2 All the symptoms of irritation are caused by spontaneous activity which appears first and foremost in the proximal part of the longest nerve fibers in the ischemic nerve The activity starts in the tactile fibers, then proceeds in the motor fibers and about the same time appears in other afferent fibers The spontaneous activity begins in from ten seconds to one and a half minutes, reaches its culmination in two to four minutes and passes off after ischemia of four to nine minutes' duration

3 Ischemia increases the excitability of the nerve This increase begins after a few seconds, reaches its culmination in about three minutes, whereupon it diminishes and, after the lapse of ten to twelve min-

22 Eccles, J. C., and Sherrington, C. S. Numbers and Contraction-Values of Individual Motor-Units Examined in Some Muscles of Limb, *Proc. Roy. Soc. London*, s. B **106** 326, 1930

23 Bjorkman, A., and Wohlfart, G. Faseranalyse de Nn oculomotorius, trochlearis and abducens des Menschen und des N. abducens verschiedener Tiere *Ztschr. f. mikr.-anat. Forsch.* **39** 631, 1936

24 Schwalbe, G. Ueber die Kaliberverhältnisse der Nervenfasern Leipzig F. C. W. Vogel, 1882

25 Kugelberg, E., and Skoglund, C. R. To be published

utes, reaches the same value as before the ischemia. The level reached by the increase is determined by factors in the blood. The smaller the amount of calcium (ionized calcium) in the blood, the higher the values, and vice versa.

4 The spontaneous activity is due to the increase of excitability of the nerve. When it reaches a certain crucial value in a given nerve fiber, spontaneous activity is produced. As shown for motor fibers, this occurs irrespective of whether the increase is produced by diminution of the blood calcium or by ischemia.

5 After preceding ischemia of the arm for ten minutes, the typical manifest symptoms of tetany induced with hyperventilation are facilitated in the same arm for about ten minutes and are then inhibited for at least an hour.

6 The attack of tetany is facilitated by a summation of the post-ischemic increase of excitability and that caused by hyperventilation, giving rise to spontaneous activity. The inhibition is due to the post-ischemic decrease of excitability.

7 The more proximal the portion of the arm which is subjected to ischemia, the more easily will the symptoms of hyperventilation tetany be induced.

8 The impulses which give rise to the symptoms of tetany in the von Bonsdorff phenomenon start first and foremost from the proximal part of the previously ischemic nerve. The focus for the attack of tetany produced by hyperventilation can thus be shifted from the proximal part of the course of the peripheral nerve distally to the desired stretch of nerve by previously subjecting the nerve to ischemia.

The sequence of the various symptoms of irritation in the spontaneous attack of tetany, the Trousseau and von Bonsdorff phenomena, is discussed in relation to the size of the fibers involved and their tendency to iterativeness on excitation with a constant current.

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## CIRCULATION OF CEREBROSPINAL FLUID IN CARASSIUS GIBELIO

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IN THE literature one finds various, and often controversial, opinions and observations concerned with the origin, movement, pathways, absorption and function of the cerebrospinal fluid. An excellent survey of this matter is found in the monograph of Katzenelbogen<sup>1</sup>. The literature gives ample proof that the formation of the fluid occurs in the choroid plexuses. Whether cerebrospinal fluid is also formed elsewhere (e.g., in the cerebrospinal parenchyma or in the ependyma) is a much debated question. According to Sepp<sup>2</sup> and others, the movement of the cerebrospinal fluid is produced by vascular pulsations, according to still other investigators, respiratory movements and movements of the body and the head are contributing factors. Concerning the relations between the cerebrospinal fluid and the perivascular and the pericellular spaces many opinions are in existence. The escape of the cerebrospinal fluid from the cerebrospinal cavity takes place by absorption into the veins, through the arachnoidal villi (Weed<sup>3</sup>), or by perineural transportation and absorption into the lymph spaces. With regard to the last point especially there exists a lively discussion.

It was the opinion expressed by Dr H. Berkelbach van den Sprenkel, conservator of this laboratory, that there is fluid in the perivascular spaces of the brain and that this cerebrospinal fluid is moved by the pulse wave of the blood vessels and consequently flows in the same direction as the blood stream. Dr Berkelbach van den Sprenkel advised me to

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From the Histological and Embryological Laboratory, University of Utrecht, Director, Prof. Dr J. Boeke.

1 Katzenelbogen, S. *The Cerebrospinal Fluid and Its Relation to the Blood*, Baltimore, Johns Hopkins Press, 1935. An extensive bibliography is included in this monograph.

2 Sepp, E. *Die Dynamik der Blutzirkulation im Gehirn*, Berlin, Julius Springer, 1928.

3 Weed, L. H. *Anatomical Consideration of the Cerebro-Spinal Fluid*, *Anat. Rec.* **12** 461, 1917, *Experimental Production of Internal Hydrocephalus*, *Contrib. Embryol.* **9** 425, 1920, *Cells of the Arachnoid*, *Bull. Johns Hopkins Hosp.* **31** 343, 1920, *Absorption of Cerebrospinal Fluid into the Venous System*, *Am. J. Anat.* **31** 191, 1923, *Effects of Hypotonic Solutions upon Cell-Morphology of Choroid Plexuses and Central Nervous System*, *ibid.* **32** 253, 1923. Weed, L. H., and Hughson. *Cerebrospinal Fluid in Relation to the Bony Encasement of the Central Nervous System as a Rigid Container*, *Am. J. Physiol.* **58** 85, 1921.

carry out experiments on fish, on the supposition that the complicated relations would be simpler to study in lower vertebrates. Nowhere in the literature have I found any communications on experiments concerned with the circulation of the cerebrospinal fluid in fish.

For my experiments I used *Carassius gibelio* (family, Cyprinidae), a kind of carp (*krioeskarpei*), a common fish in the Netherlands, about 10 cm in length. This animal proved very suitable for the experiments, since its brain is proportionally small and lies in a spacious skull. The ventricular system and the pericerebral spaces are wide so that there is relatively a great quantity of cerebrospinal fluid, moreover, the brain is not easily injured by intracranial injection.

### EXPERIMENTAL TECHNIC

*Absorption Experiments*—In this series it was tried to produce absorption of dye by letting the fish swim for varying lengths of time (one-half to forty days) in solutions of trypan blue, of various concentrations. The fish were then examined histologically to see whether the dye could be found in the central nervous system or in its membranes. These experiments are cited as series 2. For these experiments I used 8 fish, 5 of which were examined in serial sections.

*Intracranial Injections*—To trace the spread of the cerebrospinal fluid and to determine the pathways through which the fluid flows, dye was injected into the pericerebral space with a fine needle, usually in the occipital region. From 0.1 to 0.2 cc of a 1 per cent solution of trypan blue or of a 5 per cent suspension of india ink in Ringer's solution was injected. Fourteen fish were used in these experiments. Some fish died in consequence of too deep a puncture, the cerebrospinal axis having been injured. Others survived this operation, were apparently healthy and were killed at various times after the injections (twenty-three minutes to eight days). Nine fish receiving such injections were examined in serial sections.

A series of sections was also made of a normal fish which had not undergone any previous treatment.

The rest of the technical procedure was as follows.

The head was fixed in Bouin's fluid (often after removal of the lower jaw and the gills), it was then decalcified in 10 per cent trichloroacetic acid for about ten days and embedded in paraffin (via the alcohols, methylbenzoate and pyroxylin benzene, and benzene and paraffin). The resulting blocks were cut serially, and alternate sections were stained with carmalum and hematoxylin and eosin.

The body was cut in slices and also fixed, embedded, sectioned and stained. At various levels transverse sections were selected for examination.

There is no need to describe all the series of sections separately, as microscopic examination showed that the results of similar experiments were in agreement.

Experimental data on 2 fish, which are referred to later, are given here.

FISH III B—One-tenth cubic centimeter of a 1 per cent solution of trypan blue was injected intracranially in the occipital region near the median line, the fish was not very lively; it was killed twenty-four minutes after the injection.

FISH VII A—Two-tenths cubic centimeter of a 5 per cent suspension of india ink in Ringer's solution was injected intracranially in the occipital region near the median line. The behavior was fairly normal; the fish was killed eight days after the injection.

## OBSERVATIONS

## ABSORPTION EXPERIMENTS (SERIES 2)

The fish proved to be just able to stay alive when swimming in aqueous solutions of trypan blue in concentrations from 0.05 to 0.1 per cent

In more concentrated solutions they died. Histologic examination revealed the blue dye in the gills, the mucous membranes of the mouth, palate, skin canals, intestine, the blood vessels in the wall of the intestine, the myocardium, the kidneys, the periosteum of the vertebrae, and the endothelial cells of the liver and pancreas. This makes it evident that dye had been absorbed and had entered the circulating blood. Considering the blue dye in vessels of the intestinal wall, it is probable that this absorption took place in the intestine. No trace of dye was found in the central nervous system or in its membranes. Obviously, the dye did not pass through the blood-cerebrospinal fluid barrier in sufficient amounts to be detected.

That no blue dye was observed in the central nervous system is not absolute proof that a barrier exists between the blood and the cerebrospinal fluid. It is still possible that the concentration of the dye in the central nervous system was too low for the blue color to become visible.

Also using *Carassius*, Wislocki<sup>4</sup> gave intraperitoneal injections of the solutions of trypan blue. He detected the dye microscopically in the reticuloendothelial system of many internal organs (liver, spleen, kidney), in the endothelium of lymph vessels and as a diffuse blue stain of the tissues. He stated emphatically that only in the central nervous system did he fail to find any blue dye. Presumably, in his experiments the concentration of dye in the blood was higher than in mine, whereas in my fish the blue dye was in the circulation a much longer time.

As it was impossible to detect trypan blue in the central nervous system after the dye had been introduced into the circulating blood by various methods (series 2 of the present study and the experiments of Wislocki), it is permissible to conclude that in *Carassius gibelio* there exists a blood-cerebrospinal fluid barrier with respect to trypan blue.

## INTRACRANIAL INJECTION

*Pericerebral Space*—Between the brain and the skull a wide space exists. Close to the brain lies a thin membrane, containing many blood vessels. Outside this membrane is a free space, which is surrounded by a tissue extending to the skull. It was repeatedly evident

<sup>4</sup> Wislocki, G. B. Action of Vital Dyes in Teleosts, *Anat. Rec.* **12**: 415, 1917.

that there had existed connections between this tissue and the membrane surrounding the brain. Therefore the free space is to be taken, for the greater part at any rate, as the result of shrinkage.

The pericerebral tissue, extending from the membrane around the cerebrum to the skull, has a peculiar structure. It consists of flat cells, forming strands and partitions. In this manner the pericerebral space is divided into chambers and meshlike spaces. Herein lies the tissue fluid, which locally has a mucous or fatty character (Coupin<sup>5</sup>). This pericerebral tissue has a definite architecture. At the level of the olfactory tract a tissue with small chambers lies against the inner side of the skull, whereas centrally in the cranial cavity spacious cisterns are present. In general, one sees in the dorsal part of the cranial cavity a tissue with small chambers, nearer the brain the spaces are wider, next to the brain the tissue often has a meshlike structure. Lateral and basal to the brain is also wide-meshed tissue. Likewise, along the labyrinth the tissue is very delicate. At the level of the medulla oblongata it consists only of some protoplasmic strands lying in the pericerebral space. Within the first vertebral arch on the ventral side of the spinal cord a stiff fibrous tissue arises from the adventitia of the basal blood vessels in the meninx. This stiff fibrous tissue extends laterad and dorsad until the cord lies enclosed in a close-fitting shell (fig 6*F*). At this point the meshlike tissue has nearly disappeared. About 500 microns more caudal the fibrous tissue is again found in only the ventral region. Now the cord lies once more in the usual meshlike tissue.

From the injection of dye into the pericerebral tissue it was ascertained that the dye spreads swiftly through the chambers and meshes of the pericerebral tissue. This spread was swiftest and the dye most dense where the tissue was of a meshlike structure or where the tissue chambers were spacious—consequently near the brain. Yet I noted repeatedly in animals killed about twenty minutes after the injection that in the small chambers near the skull the coagulum of the mucous tissue fluid was already blue throughout. Hence, injected dye spreads quickly through the pericerebral tissue. It is evident, therefore, that many opportunities exist for exchange of fluids in the meshes and chambers in the various parts of the tissue lying between the brain and the skull.

In all animals it was obvious that the dye injected into the pericerebral tissue, spread immediately through the whole ventricular system, the roof of the fourth ventricle not having been injured by the injection. Thus it is evident that an extensive exchange of fluid must take place between the ventricular system and the meshes and chambers of the pericerebral tissue.

<sup>5</sup> Coupin, F. Les formations choroïdiennes des poissons, *Arch de morphol gen et exper*, 1924 no 20, pp 1-156

The particles of dye in part lay free in the ventricles and in the spaces of the pericerebral tissue and in part were phagocytosed by histiocytes. In determining the spreading of the dye, one has to take into consideration that histiocytes, having phagocytosed the particles of dye, can wander everywhere. Only the spread of free dyestuff gives an indication of the spread of cerebrospinal fluid.

Thus, the experiments with intracranial injection prove that a close connection exists between the ventricular fluid and the contents of the meshes and chambers of the pericerebral tissue, that the meshes and chambers of this tissue communicate with each other and that fluid can flow through them. Hence, the relations in *Carassius gibelio* are in principle the same as those in higher vertebrates. The ventricular system contains a fluid (liquor internus), and the brain is surrounded with a fluid (liquor externus), which flows through the meshes of the pericerebral tissue (meninx). This pericerebral fluid and the ventricular fluid are closely related.

Ariens Kappers,<sup>6</sup> in agreement with Steiner, spoke of a meninx primitiva in teleosts, since he found no differentiation of pia, arachnoid and dura in these forms and the meshlike tissue has no endothelial covering, as exists in a true arachnoid. Between the skull and this meninx primitiva he still discerned a perimeningeal tissue, and in some teleosts (*Lophius*) he described a kind of dual membrane as well.

In an extensive treatise, van Gelderen<sup>7</sup> explained that in most teleosts an ectomeninx lines the skull and an endomeninx covers the brain and that between them lies an intermeningeal tissue, of a mucous or fatty character. I found the pericerebral tissues of *Carassius* to be in accordance with this description.

Ariens Kappers<sup>6</sup> also stated emphatically that as there is no arachnoid there can be no external fluid. This last opinion one encounters repeatedly in the literature (Coupin, among others). To my mind, Ariens Kappers is in error in refusing to call the fluid which flows in the meshes and chambers of the pericerebral tissue, and which is closely related to the ventricular fluid, liquor externus because the tissue morphologically does not quite correspond with the arachnoid. Even if the pericerebral tissue does not quite correspond morphologically with the leptomeninges of the higher vertebrates, it has no doubt the same

6 Ariens Kappers, C. U. Meminges in Lower Vertebrates, *Arch. Neurol. & Psychiat.* **15** 281 (March) 1926. Ariens Kappers, C. U., Huber, G. C., and Crosby, E. C. *Comparative Anatomy of the Nervous System of Vertebrates, Including Man*. New York, The Macmillan Company, 1936.

7 van Gelderen, C. Ueber die Entwicklung der Hirnhäute bei Teleostiern, *Anat. Anz.* **60** 48, 1925. Die vergleichende Ontogenie der Hirnhäute, mit besonderer Berücksichtigung der Lage der neurokranialen Venen, Thesis, Amsterdam, Munich, J. F. Bergmann 1926.

significance. Therefore, I shall designate as meninx all the tissue between the skull and the brain in the meshes and chambers of which flows a fluid in close relation to the ventricular fluid. The meshes and chambers together constitute the meningeal space.

*Roof of the Fourth Ventricle*—Although apparently an extensive exchange of fluid takes place between the internal and the external fluid, the roof of the fourth ventricle seems to be continuous, and no open foramen (of Magendie or of Luschka) is found here. But at various places in this region the roof has become a very thin membrane, outwardly consisting of the inner meningeal membrane and inwardly lined with ependyma. The ependyma is very flat here, and at many places it cannot be decided whether an ependymal lining still exists or whether the few flat cells which form the roof are meningeal. However, in some places the ependymal lining is plainly interrupted for some distance, so that actually the ventricular roof consists of meninx only. Hence, if the meninx were taken away, openings would be left in the roof. It is probable that this very thin roof gives opportunities for the exchange of fluid between the ventricle and the meningeal space (fig. 5 H).

*Roof of Third Ventricle*—That connections exist elsewhere between the ventricle and the meningeal space was apparent, among other specimens, in fish III B. The greater part of the roof of the third ventricle was very thin and consisted almost exclusively of ependyma outwardly covered by the inner membrane of the meninx. At many places blue lines were seen between the high ependymal cells, therefore a continuity existed between the blue coloring matter in the ventricle and that in the meningeal meshes. I observed this, for example, at the level of the corpora striata and close to the tori longitudinales, just anterior to the cerebellum. Of course, my sections do not answer the question about the direction of passage of the fluid through the roof, but they do prove that at these places communication exists between the internal and external cerebrospinal fluid (fig. 5 K).

The roof of the third ventricle is lined with several kinds of ependymal cells. (It is strange that nothing can be found about these various forms of ependyma in Coupin's article, notwithstanding his extensive study of the ventricular roofs and plexuses in fishes.) Laterally the ependymal cells are very flat (although not so flat as those in the roof of the ventricle), medially there is a region with high cylindric ependymal cells. Close in front of the posterior commissure a tube arises from the roof. This tube extends forward in the median line and at the level of the bulb olfactorius becomes a flat organ, lying close under the skull. This organ is the epiphysis cerebri (Brachet<sup>8</sup>).

<sup>8</sup> Brachet A. *Traité d'embryologie des vertebres* ed. 2, Paris: Masson & Cie 1935 p. 376.

*Choroid Plexus of Third Ventricle*—In front of the pineal tube the roof is strongly folded, and it projects dorsally as a sac which encloses the pineal tube. This sac is the choroid plexus of the third ventricle. Its walls have many folds and are lined with a cuboid, or simply a cylindric, epithelium, often with vacuoles at the apex. The bases of the epithelial cells border immediately on the walls of many wide capillaries, which are lying here in the meninx. Repeatedly, the capillaries project into the epithelial layer between the cells, so that the lumen of the blood vessel and the space in the plexus sac are separated only by an extremely thin strip of protoplasm. I found such interepithelial capillaries also in the pineal tube and in the medial part of the roof of the third ventricle.

*Choroid Plexus of the Fourth Ventricle*—This structure lies medially in the ventricular roof. The roof here is folded, and the folds hang downward in the ventricle. The epithelium of the plexus is cylindric, and the cells are somewhat higher than those in the plexus of the third ventricle. Immediately beneath the epithelial layer, many blood vessels lie in the meninx which accompanies the folds.

*Absorption in Choroid Plexus*—From the literature, it is apparent that the formation of the cerebrospinal fluid occurs in the choroid plexus. Some authors think that absorption occurs also in the plexus. My sections give support to this last opinion.

In fish III B, many veins of the choroid plexus of the fourth ventricle which lay against the epithelial layer contained a strongly blue-stained coagulum of plasma, whereas in the immediate vicinity of these veins no important concentration of dye was seen. In other veins, in the meninx, one seldom saw such a blue coagulum, and then only when much dyestuff was lying in the surrounding meningeal tissue.

In fish VII A the epithelial cells of the plexus of the fourth ventricle which were lying in the tops of the folds contained a considerable number of india ink granules, (fig 1 and fig 5 J). The cells that contained the granules were those cells which were chiefly in contact with the ventricular fluid and so had the best opportunity of absorbing carbon particles from the internal cerebrospinal fluid. The assumption of absorption appears to me to be the only possible explanation of this peculiar distribution of the granules in the epithelium of the plexus, and the local accumulation of trypan blue in the veins is difficult to explain in any other way.

As to the choroid plexus of the third ventricle, my sections are less convincing. In fish VII A, the epithelium of the plexus of the third ventricle contained much less carbon than that of the plexus of the fourth ventricle yet there were also fine carbon granules in the epithelium of the plexus sac, much finer than in the plexus of the fourth ventricle. Also, in the roof of the third ventricle similar fine

particles were to be found in the flat, as well as in the high, ependymal cells. On the inner and on the outer side of the roof of the third ventricle, as well as in the ventricle itself and in the meningeal space, carbon particles were lying. Consequently, it is not possible to decide whether the granules in the ependymal cells were absorbed from the internal cerebrospinal fluid or whether they were carried from the meninx to the ventricle. In fish III B, a blue hue was noted in some of the veins of the plexus and in the ventricular roof.

I think that it is permissible to conclude, therefore, that the epithelial cells of the choroid plexus of the fourth ventricle absorb colloidal particles from the internal cerebrospinal fluid and release these particles into the blood. My sections do not permit a conclusion as to

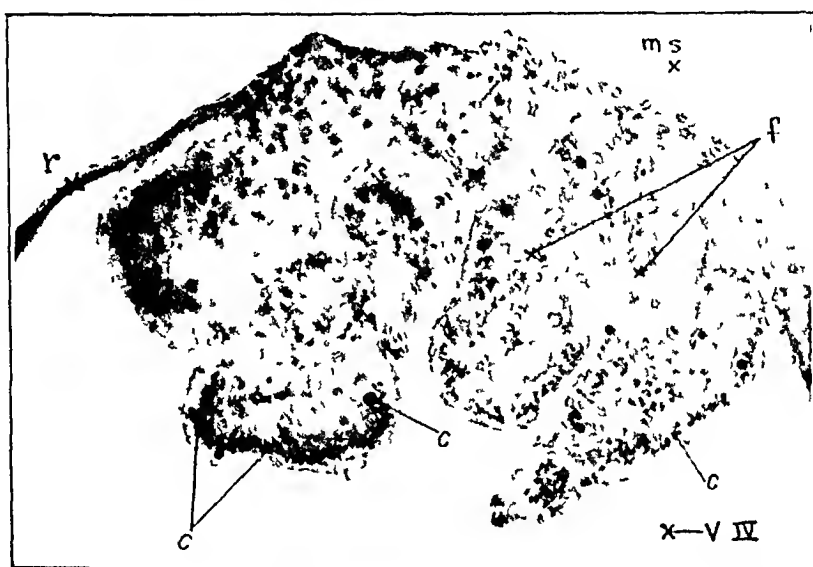


Fig 1 (fish VII A, section 72, I, 6) —Section (about  $\times 400$ ) showing the choroid plexus of the fourth ventricle

Here, *ms* indicates the meningeal space, *r*, the thin roof of the fourth ventricle, lined with low ependymal cells, *f*, folds of the roof, covered with high epithelial cells and hanging into the ventricle, *V IV*, lumen of the fourth ventricle, and *c*, carbon particles stored in the epithelial cells.

It is evident that the dye is stored in those epithelial cells that are most in contact with the ventricular fluid. Probably absorption from the internal cerebrospinal fluid takes place in these cells (cf fig 5 J).

whether particles are absorbed from the cerebrospinal fluid by the choroid plexus and by the roof of the third ventricle.

*Perivascular Spaces* —The blood vessels in the brain are surrounded by spaces which are continuations of the pericerebral space. Like the meningeal space, these perivascular spaces are traversed by fine tissue strands, so that they have a meshlike structure. The perivascular spaces are also distinctly visible around the small vessels, but it cannot be decided whether or not they are still virtually present around the smallest vessels and capillaries.



In all my specimens, communication existed in many places between the ventricular space and the perivascular spaces of vessels lying just beneath the ependyma. This communication was effected by interruptions in the ependymal layer. The blood vessels were then often nearly intraependymal. These open communications were most distinct in the optic tectum. It is evident that these communications gave opportunity for the exchange of fluid between the internal cerebrospinal fluid and the contents of the perivascular spaces. This exchange was demonstrated by the intracranial injections.

It was observed repeatedly that the dye had penetrated from the ventricular space through the open communications into the perivascular space of the subependymal blood vessels. It is apparent, especially in the case of the carbon granules, that the particles of dye were carried along in the perivascular spaces in the same direction as that in which the blood flowed in the vessel. If one follows an artery whose perivascular space communicates with the ventricle, beginning at the point of this communication and going downstream, one still sees carbon particles lying around the vessel and its branches in many sections after the artery has left the neighborhood of the ventricle. Sometimes 40 sections (of 10 microns each) beyond the point of communication dye is still present in the periarterial space. If one follows this artery in the opposite direction, or upstream, it appears that the dye has hardly been carried along at all. Three or four sections in front of the communication of the ventricle with the perivascular space there are no longer any carbon particles around the vessel (fig 5 *F*). Hence, the dye particles have been carried in the perivascular space in the same direction as that in which the blood flows in the vessel, whereas no dye has been carried in the opposite direction.

I saw a similar picture around veins. In fish VII A, several venous branches in the optic tectum joined and formed a small vein, just beneath the ependyma. Soon there was an open communication between the ventricle and the perivenous space. Here the ventricle contained many carbon particles, which entered the perivenous space at the point of communication and from there were seen around the vessel. Then the vein left the region of the ventricle and passed through the optic tectum, still surrounded with dye. Then, it opened into the venous network of the meninx on the surface of the brain, while the perivascular space opened into the meningeal space (fig 5 *E*). Here, therefore, the perivenous space formed a direct junction canal between the ventricle and the meningeal space, and, again, dye was carried in the direction of the blood current, that is, from the ventricle to the meninx. Of course, all the periarterial spaces which communicate with the ventricle also form such junction canals. In these spaces the fluid flows from the meninx to the ventricle (fig 5 *C*).

It is curious that in all my fish arteries were observed lying just beneath the ependyma, these gave off branches penetrating the ependymal layer. These arterial branches ran right through the ventricular space toward the cerebellum, which projects here into the ventricle. They entered the cerebellum, where they ramified. At the point where they passed through the ventricular space these arteries were not covered with an ependymal layer. Ventricular fluid flowed around the adventitia. The perivascular spaces of these arteries opened into the ventricle where the vessels passed from the cerebrum into the ventricle and where the vessels left the ventricle and entered the cerebellum. Here, too, in fish VII A, carbon particles were carried from the ventricle into the perivascular spaces in the direction of the blood current, and so into the cerebellum (fig 5 G). Charlton<sup>9</sup> gives a figure showing a transventricular blood vessel in a viper. He did not mention the behavior of the perivascular space.

It has already been noted that the perivascular spaces communicate with the meningeal space (page 530), being, as it were, continuations of the latter. It is obvious that the external cerebrospinal fluid and the perivascular fluid are closely related. The transportation of particles of dye here is interesting. They penetrated from the meningeal space into the perivascular spaces of arteries entering the brain and were observed deep in the cerebrum around these vessels and their branches. Here, too, then, dye was transported in the direction of the blood current (fig 2 and fig 5 B). In the perivascular spaces of veins leaving the brain and entering the meninx no dyestuff was found (fig 5 D) unless the perivascular space of the vein had been in connection with the ventricle (fig 5 E). The blood current here is directed outward from the brain, and into the spaces around these veins no dye penetrates, for this would be against the blood stream.

In résumé, the following facts concerning the perivascular spaces were noted

- 1 Spaces surround the vessels in the brain of *Carassius gibelio*
- 2 These perivascular spaces are in open communication with the meningeal space and with the ventricle
- 3 Particles (of india ink or typan blue) in colloid suspension in the external or the internal cerebrospinal fluid pass through these communications from the meningeal space or the ventricle into the perivascular spaces
- 4 These particles are carried along in the perivascular spaces in the same direction as that in which the blood flows in the vessels

<sup>9</sup> Charlton, H. H. Gland-Like Ependymal Structure in the Brain, *Proc Kong Akad van Wetenschappen* 31 823, 1928

From these observations, it is evident, that the particles move from the ventricle and the meningeal space through open communications into the perivascular spaces and are carried along in these spaces, one may conclude that the cerebrospinal fluid follows the same course. The vessels in the brain are therefore surrounded with cerebrospinal fluid, which moves in the same direction as the blood in the vessels and which is in direct connection with the external cerebrospinal fluid,

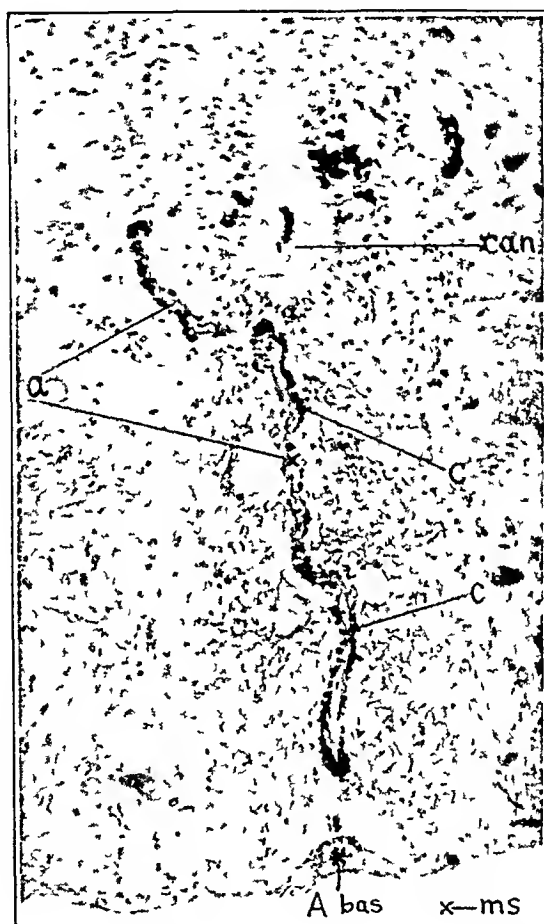


Fig 2 (fish VII A, section 53, II, 2) —Transverse section (about  $\times 400$ ) through medulla oblongata

Here, *can* indicates central canal, containing dyestuff, *ms*, meningeal space, *A bas*, basal artery, *a*, branch of basal artery, penetrating the nervous tissue, *c*, carbon particles in the perivascular space, carried along in the same direction as the blood stream (cf fig 5 B and C)

around the brain, and with the internal cerebrospinal fluid, in the ventricle

*Passage of the Cerebrospinal Fluid*—No special apparatus for absorption of cerebrospinal fluid comparable with the arachnoidal villi of higher animals (Weed<sup>3</sup>), was found here. The absorption

of particles from the internal cerebrospinal fluid in the choroid plexus of the fourth ventricle has already been mentioned. Microscopic examination of the specimens revealed many places where the passage of cerebrospinal fluid from the cerebrospinal cavity might take place.

**Cervical Region** The pericerebral space is most pronounced at the level of the first three cervical vertebrae. At the junction of the



Fig 3 (fish VII A, section 34, I, 1) —Transverse section (about  $\times 10$ ) through the spinal column at level of the first vertebral arch (cf fig 6 G)

Here, *va* indicates the vertebral arch, *cv*, the vertebral body, *med*, the cervical portion of the cord, *m*, meningeal tissue, *me*, extravertebral meninx, *mo*, outer layer of the meninx, *mu*, muscle, *c*, accumulations of dye (carbon particles) in the extravertebral continuations of the meningeal space (fig 6 B)

skull and the spine the pericerebral space is laterally no longer enclosed by bone or cartilage, here, there is a wide aperture in the bony case, where the meningeal space is separated from the dorsal musculature only by the thin, pigmented outer layer of the meninx. The first

spinal nerve, here, is composed of a dorsal and a ventral root. The spinal ganglion lies in the meshlike meninx. The outer layer of the meninx has an aperture through which the spinal nerves and blood vessels leave the meningeal space. The meshlike meninx around these nerves and vessels merges with the loose connective tissue, which accompanies them farther.

Somewhat more caudally the spinal cord is surrounded by the first vertebral arch. This arch, however, is too narrow to enclose the whole meningeal space, laterally, part of this space lies outside



Fig. 4 (fish VII A, section 18, II, 6) — Transverse section (about  $\times 10$ ) through the spinal column at level of the third cervical nerve (cf fig 6 H).

Here, *va* indicates vertebral arch, *cv*, vertebral body, *med*, cervical portion of cord, *m*, meningeal tissue, containing carbon particles, *dr*, dorsal root of third cervical nerve, *vr*, ventral root of third cervical nerve, *g*, ganglion, *mu*, muscle, *c*, accumulation of dye (carbon particles) in paravertebral connective tissue.

The roots of the third cervical nerve leave the vertebral canal here through an aperture between the vertebral arch and the vertebral body, the foramen intervertebrale. The meshlike meningeal tissue is in contact with the perivertebral connective tissue, but there is no sharp division between them. Dye has been carried from the meningeal space into the connective tissue beside the spinal column.

the arch. This extravertebral continuation of the meningeal space is carried caudally for a distance of several vertebral arches. It is separated from the surrounding muscular and connective tissue by

the outer layer of the meninx (fig 6 *B* and fig 3) At the ventral side, however, this outer layer disappears, and the extravertebral meningeal tissue is in direct contact with the loose connective tissue, which reaches along the body of the first vertebra ventrally and contains a number of veins It is not possible to mark exactly the partition between the meninx and the connective tissue Certainly, it gives the impression that the external cerebrospinal fluid can be carried here into the connective tissue

Within the first vertebral arch the spinal cord is enclosed in the fibrous shell (see page 525 and fig 6 *F*), somewhat more caudally the cord is again surrounded by the usual meshlike meninx Close around the cord there is now a pigmented membrane

Beneath the first vertebral arch the second set of cervical roots arises The roots join in the extravertebral meninx, where the spinal ganglion also lies The pigmented membrane which encloses the spinal cord continues around the spinal roots, the ganglia and the nerves The spinal nerves, accompanied with blood vessels, enter the paravertebral connective tissue Here, too, no sharp division between meninx and connective tissue can be found, and, again, the passage of the external cerebrospinal fluid into the connective tissue is not improbable These relations are nearly the same with the next set of cervical roots, but the extravertebral meningeal space becomes smaller here

At the level of the fourth set of cervical roots, as well as of the following sets, however, no meshlike tissue lies along the spinal column The spinal ganglion now lies exactly in the intervertebral foramen, thereby practically filling it The meshlike meninx is not in contact with the loose connective tissue here It does not seem probable that the cerebrospinal fluid can still pass into the connective tissue here (fig 6 *E*)

The intracranial injections proved that cerebrospinal fluid indeed leaves the cerebrospinal cavity at the places where on microanatomic grounds the passage of cerebrospinal fluid was presumed to take place Accumulations of dye were found in the extravertebral meninx The dye had spread from the meningeal space into the perineural and perivascular loose connective tissue, where the outer layer of the meninx lets the spinal nerves and vessels through

In the specimens in which injections of trypan blue were made the fibers of connective tissue around the first three cervical nerves were colored blue to a considerable distance from the spine Many histiocytes carrying granules of dye lay in this connective tissue In many blood vessels in this connective tissue were blue-stained endothelial cells, and sometimes a few cells with a blue protoplasm lay

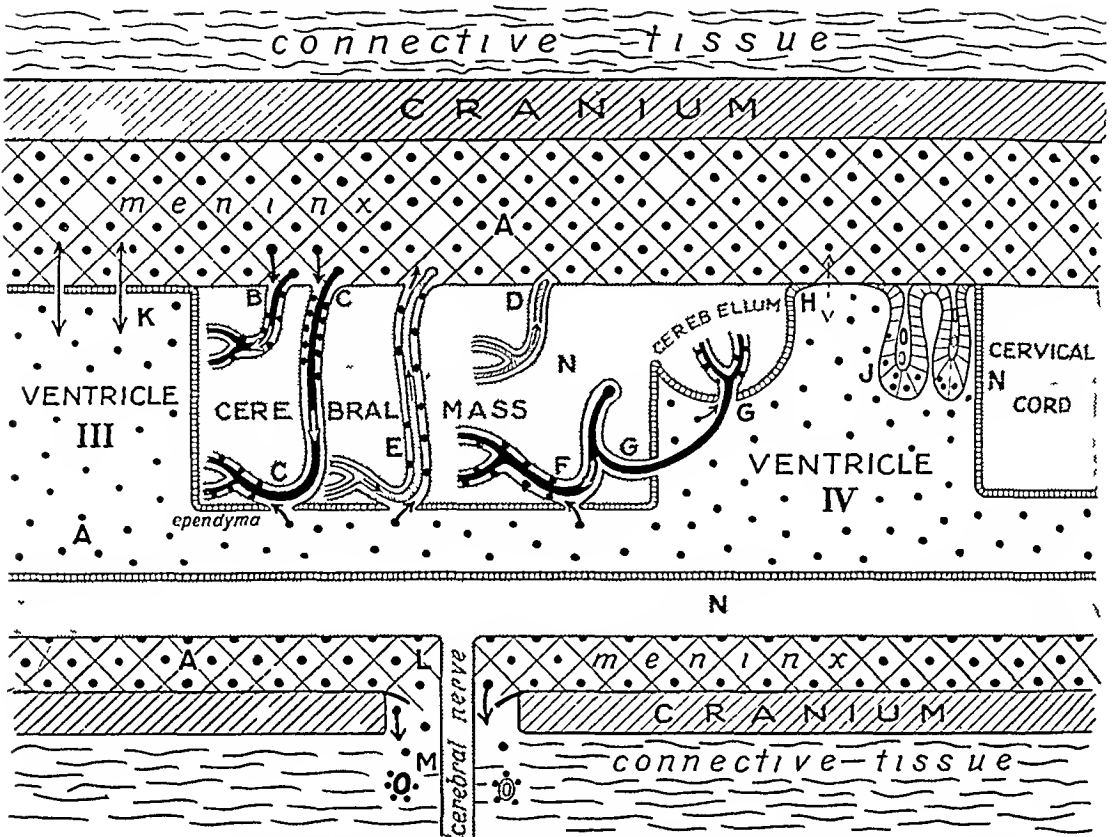


Fig 5—This diagram represents a sagittal section through the brain. Arteries are shown in solid black, veins, in hatchure, and dye particles, as dots in india ink.

(A) The injected dye spreads through the whole meningeal space and through the ventricles. (B-F) The blood vessels in the brain are surrounded by perivascular spaces. (B) An artery projects from the meninx into the brain. In its perivascular space dye is carried along in the same direction as the blood stream. (C) An artery runs from the surface of the brain to the ventricle. Its perivascular space forms a junction canal between the meningeal space and the ventricle. Dye is carried in the perivascular space in the same direction as the blood stream. A continuous row of particles from the meninx to the ventricle has not yet been formed, and the dye has penetrated only halfway. (D) A vein leaves the brain. The space around the vessel opens into the meningeal space. No dye has penetrated here (it would have been against the direction of the blood current!). (E) The perivascular space of a vein communicates with the ventricle and later opens into the meningeal space. Dye is transported here right through the brain, from the ventricle to the meningeal space. (F) An artery lies just under the ependymal layer. The perivascular space is in open communication with the ventricle. Through this communication dye penetrates into the perivascular space and is carried downstream. (G) An arterial branch goes right through the ventricle and enters the cerebellum. Its perivascular space communicates with the ventricle. Dye particles are carried along in the perivascular space and move in the direction of the blood stream. (H) In the roof of the fourth ventricle no open foramen exists. The roof, however, is extremely thin, locally, the ependymal layer is interrupted, and the roof consists of meninx only. Probably, possibilities for the exchange of fluid are present here. (I) The high epithelium of the choroid plexus of the fourth ventricle contains carbon particles, just where contact with the ventricular fluid is best. At the base of the epithelium lie many blood vessels (in fish III B, containing blue coagulums). There is absorption of colloidal particles from the internal cerebrospinal fluid. (K) Through the roof of the third ventricle communication exists between the ventricular fluid and the meningeal fluid (blue lines through the roof between the ependymal cells after injection of trypan blue!). (L) A cranial nerve arises from the brain and leaves the cranial cavity through a foramen in the base of the skull. (M) Along this nerve the meninx merges with the extracranial connective tissue. Dye escapes from the meninx into the connective tissue and is here transported in adventitial lymph spaces. (N) No dyestuff is to be seen in the cerebral parenchyma.

loose in the lumen of the vessel. It was the same with the connective tissue extending from the region ventral to the spinal cord, along the first vertebra, to the extravertebral meninx. The spread of the carbon particles was analogous. These, too, were partly stored in histiocytes, but free particles were frequently noted in the connective tissue, especially immediately around blood vessels, in the adventitial

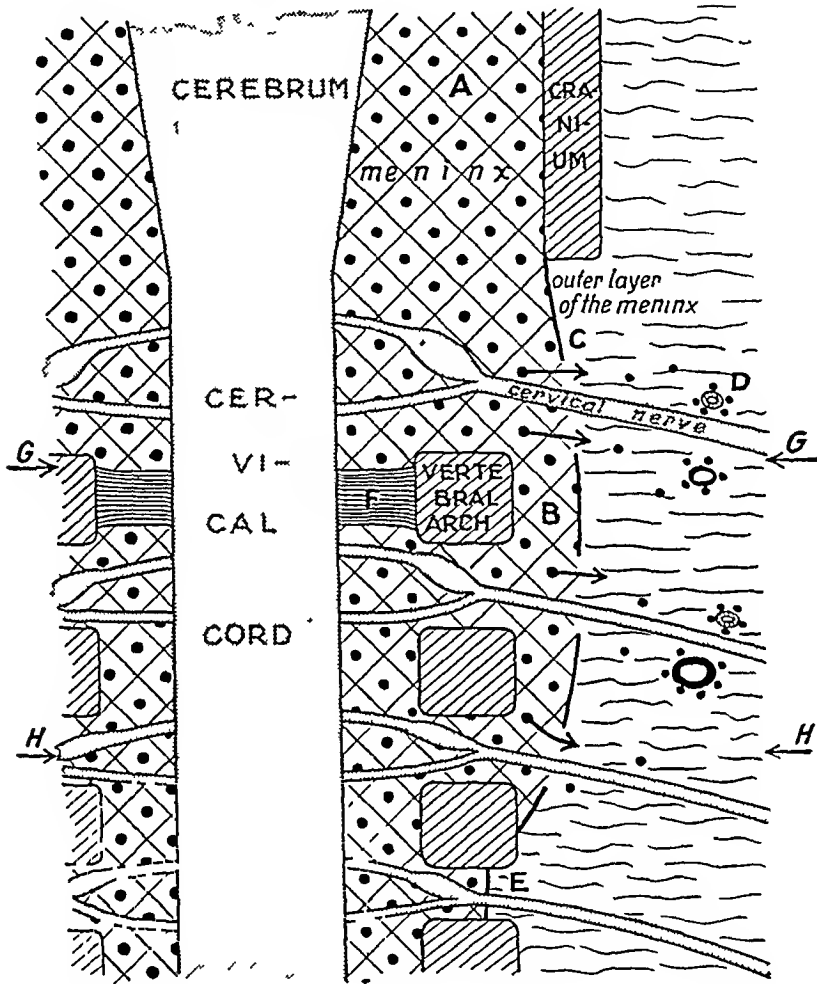


Fig 6—This diagram represents the cervical portion of the cord and its surroundings

(A) The meninx contains particles of dye in its meshes. (B) Outside the first three vertebral arches lies part of the meningeal space, the arches being too narrow to enclose the whole meningeal space. This extravertebral meninx contains much dyestuff. (C) Along the first three cervical nerves the extravertebral meninx merges with the connective tissue. Dye leaves the meningeal space here and enters the connective tissue. (D) Dye is transported in adventitial lymph spaces. (E) No passage of dye takes place at the level of the fourth cervical nerve. The extravertebral meninx has ended here. (F) Inside the first vertebral arch the meningeal space is filled with a stiff fibrous tissue, enclosing the cord as a shell. (G) Level of the transverse section shown in figure 3. (H) Level of the transverse section shown in figure 4.

lymph spaces. This transportation of dye took place along the first three sets of cervical roots (figs 4 and 6). More caudally I saw no spread of dye from the meningeal space into the connective tissue (fig 6 E).



Therefore the dye was not only removed from the meningeal space by histiocytes but was also transposed without having been stored in cells (blue fibers of the connective tissue and free carbon particles in the tissue clefts and lymph spaces) This proves that cerebrospinal fluid, too, must have flowed here from the meningeal space into the connective tissue In the region of the first three cervical nerves, therefore, external cerebrospinal fluid is carried from the cerebrospinal cavity into the surrounding connective tissue

**Cranial Region** In the cranial region, too, several possibilities for the transportation of cerebrospinal fluid were found Some cerebral nerves leave the skull through wide apertures in which the meshlike meninx and the extracranial connective tissue are in contact with each other Here, too, one cannot mark a sharp division between them, and here, too, passage of the cerebrospinal fluid seems possible This is especially noticeable along the olfactory nerves and the optic chiasm

Indeed, the injected dye evidently spread from the meningeal space into the spongy connective tissue, which, outside the skull, surrounds the cerebral nerves (fig 5 *L, M*) Hence, the dye was carried through the foramina at the cranial base and was still visible at a considerable distance from the skull, e g, immediately under the olfactory epithelium Here, too, the pathways for the transportation of dye lay mainly in the adventitia of the blood vessels Again, trypan blue was noted in histiocytes and gave a blue hue to the connective tissue, carbon particles were also seen as free corpuscles in the tissue, where they often lay in rows, thereby indicating the course of the tissue clefts and the lymph pathways

This transportation of dye was distinct along the olfactory nerves and the optic chiasm, but also along the trigeminal nerve I sometimes found undeniable signs of dye escaping from the meningeal space into the extracranial connective tissue Hence, it is evident that in the cranial region, too, dye was carried from the cerebrospinal cavity at those places where on microanatomic grounds it was assumed that drainage of the cerebrospinal fluid exists, to wit, where the meshlike meninx is in contact with loose connective tissue The transportation of free dye not stored in cells proves that here, too, the cerebrospinal fluid must have left the meningeal space along the same pathways

The transportation of external cerebrospinal fluid from the meningeal meshes therefore occurs along the olfactory nerve, the optic chiasm, the trigeminal nerve and in the region of the first three cervical nerves

One may expect that transportation of the dye particles through the tissue clefts and the lymph passages will finally bring them into the blood Indications that the dye has actually reached the blood

were observed in both fish III B and fish VII A. In fish III B I observed blue endothelial cells in the liver and in fish VII A I noted accumulations of carbon particles in a lymphoid part of the liver and some granules in the interstitial tissue of the kidney.

*Cerebrospinal Parenchyma*—Only exceptionally was dyestuff seen in the cerebrospinal parenchyma. In fish III B, blue-stained parenchyma was noted in the olfactory tracts, around the sylvian aqueduct and in the floor of the fourth ventricle. Blue-stained glial fibers were seen here. In the corpora striata of fish VII A carbon particles were observed in the parenchyma just under the ependyma (in symmetric sites to the right and to the left). Generally, however, the parenchyma was not colored, not even near those ventricular, perivascular or meningeal spaces which contained much dyestuff.

That intracranial injection of dye leaves the parenchyma uncolored is a common observation (Goudsmit,<sup>10</sup> Dewey<sup>11</sup>). Hence, between the cerebrospinal parenchyma and the internal, perivascular and external cerebrospinal fluid there also exists a barrier, although it is not an absolute one. Stern's<sup>12</sup> statement that no barrier exists between the cerebrospinal fluid and the parenchyma seems to me inaccurate, at least for the fish used in this study. To my mind, there exists a barrier between the blood and the cerebrospinal fluid (*barrier I*), as well a barrier between the cerebrospinal fluid and the parenchyma (*barrier II*). The blood-cerebrospinal fluid barrier (*I*) lies in the walls of the blood vessels and in the choroid plexus, the cerebrospinal fluid-parenchyma barrier (*II*) lies in the ependyma (with respect to the ventricular fluid), in the *membrana limitans gliae perivascularis* (with respect to the perivascular cerebrospinal fluid) and in the *membrana limitans gliae superficialis* (with respect to the external cerebrospinal fluid) (fig. 8).

#### SCHEMATIC SYNOPSIS

In figures 5 and 6 I have collected the most important of my observations. The facts shown here diagrammatically have been described in the text and are briefly noted in the explanations of the schemas.

<sup>10</sup> Goudsmit, J. Experimental Investigations with Trypan Blue, Thesis, Amsterdam, 1920.

<sup>11</sup> Dewey, K. W. Contribution to the Study of the Pathways of the Cerebrospinal Fluid and the Choroid Plexus, *Anat. Rec.* **15** 1, 1918.

<sup>12</sup> Stern, L. La barrière hémato-encéphalique en physiologie et en clinique, *Schweiz. med. Wchnschr.* **53**:792, 1923. Stern, L., and Gautier, R. Recherches sur le liquide céphalo-rachidien, *Arch. internat. de physiol.* **17** 138 and 391, 1921, **20** 403, 1923.

## COMMENT

21

My observations prove experimentally that in *Carassius gibelio* the cerebrospinal fluid in the perivascular spaces flows in the same direction as the blood. This movement of the cerebrospinal fluid must be caused by the pulse wave. Hence, the heart furnishes the driving power for the intracerebral movement of the cerebrospinal fluid. These facts confirm for *Carassius gibelio* the hypothesis of Sepp and Berkelbach van den Sprenkel, who concluded on theoretic grounds that movement of the cerebrospinal fluid is produced by the pulse wave.

I have not been able to prove the existence of perivascular spaces around the capillaries, and the dye has nowhere penetrated so far. I cannot decide whether the perivascular spaces actually end in the precapillary regions or whether they are still virtually present around the capillaries. Diagrammatically, one can imagine that the movement of perivascular fluid occurs as follows (fig. 7).

The pulse wave in the artery massages the cerebrospinal fluid deeper into the perivascular space. There are three now possible courses for the fluid:

1 The cerebrospinal fluid penetrates into the parenchyma (*A*). This penetration, if present, must be controlled by the cerebrospinal fluid—parenchyma barrier (*barrier II*). At the same time, fluid will leave the parenchyma and enter the perivascular spaces of the venous system (*D*).

2 The cerebrospinal fluid is absorbed into the blood (*B*).

3 If spaces are still virtually present around the capillaries it will be possible for the cerebrospinal fluid to move along the capillaries to the spaces around the venous system (*C-E*).

In my experiments the particles of dye did not penetrate far enough in the perivascular spaces of the small arteries to make it possible to decide which of these three theoretically possible courses actually is followed by the cerebrospinal fluid. My sections prove only that the perivascular cerebrospinal fluid moves in the same direction as the blood in the vessel, hence, I think, the pulse wave must be the driving power for this movement.

That communications between the perivascular spaces and the ventricle were regularly found is essential to the conception of the circulation of cerebrospinal fluid in fishes. In the literature I found no observations on such open communications.

Nowhere did I see perivascular spaces communicating with pericellular spaces, as described by Mott<sup>13</sup>. Moreover, the dye was

<sup>13</sup> Mott, F. W. The Oliver-Sharpey Lectures on Cerebrospinal Fluid, *Lancet* 2 1 and 79, 1910.

never observed to reach these pericellular clefts, which I look on as artefacts (Gadnat<sup>14</sup>) In figure 8, finally, the relations between the blood, the cerebrospinal fluid and the cerebrospinal parenchyma are shown as I have conceived them to be in *Carassius gibelio*, on the basis of the observations described here

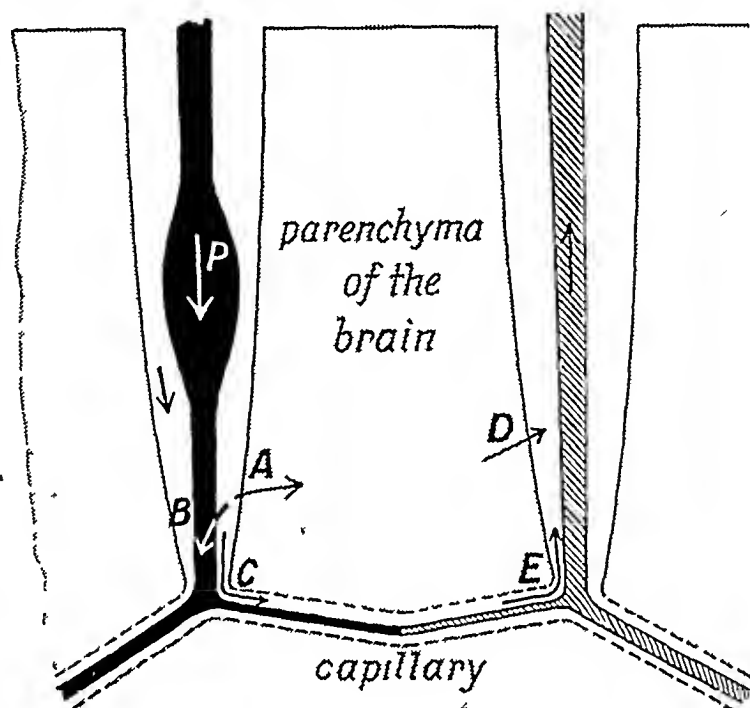


Fig 7 (partly after Sepp<sup>2</sup>)—On consideration of what happens to the perivascular cerebrospinal fluid in the precapillary region when it is driven by the pulse wave (*P*) deeper into the periarterial space, three possibilities suggest themselves 1 The cerebrospinal fluid may leave the periarterial space and enter the parenchyma (*A*) Simultaneously, fluid will leave the parenchyma and flow into the perivenous spaces (*D*) 2 The cerebrospinal fluid may pass through the wall of the vessel (*B*) and be absorbed into the blood 3 If perivascular spaces are still present around the capillaries, it will also be possible for the cerebrospinal fluid to reach the perivascular spaces of the venous system (*C-E*) by this route

#### SUMMARY

From this microscopic study of *Carassius gibelio*, especially after intracranial injections of dyestuff, the following conclusions may be drawn

- 1 Perivascular spaces accompany the blood vessels in the brain
- 2 These perivascular spaces are in open communication with the meningeal meshes and with the ventricular space
- 3 The perivascular spaces contain cerebrospinal fluid This perivascular cerebrospinal fluid is in direct communication with the

<sup>14</sup> Gadnat, J De l'espace périvasculaire du cerveau et de la moelle, Paris, J B Baillière et fils, 1931

internal cerebrospinal fluid, in the ventricle, and with the external cerebrospinal fluid, in the meningeal spaces

4 The perivascular cerebrospinal fluid moves in the same direction as the blood stream in the vessels. This movement is caused by the pulse wave

5 Transventricular arteries are regularly present

6 The ventricular system contains cerebrospinal fluid (internal cerebrospinal fluid), the brain is surrounded with cerebrospinal fluid (external cerebrospinal fluid), lying in the meshes and chambers of the meningeal tissue

7 An extensive exchange of fluid occurs between the internal and the external cerebrospinal fluid, as shown by the rapid spread

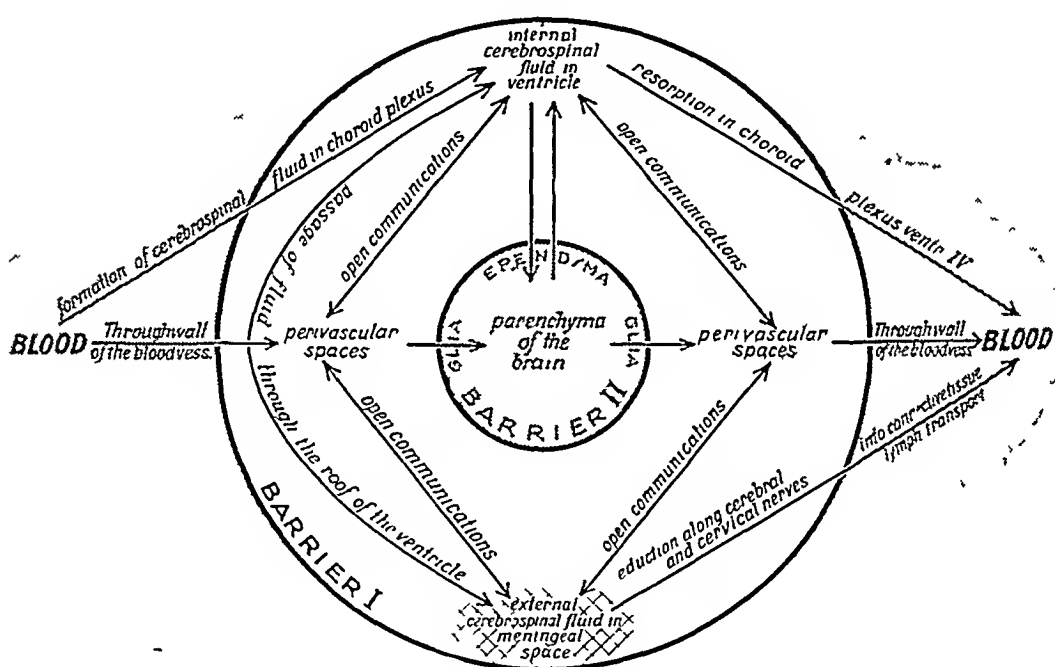


Fig 8—Probable relations of the blood, the cerebrospinal fluid and the cerebrospinal parenchyma in *Carassius gibelio*

It is to be noted (1) that there is always cerebrospinal fluid between the blood and the parenchyma, (2) that selective barriers separate the cerebrospinal fluid from the blood and the parenchyma from the cerebrospinal fluid, and (3) that ventricles, meningeal space and perivascular spaces form one communicating system, containing the cerebrospinal fluid

through both of dye injected into the pericerebral spaces. This exchange of fluids occurs (a) through the thin roof of the third ventricle and (b) through the perivascular spaces of vessels reaching the surface of the brain from the ventricle

8 The roof of the fourth ventricle has no open foramen. This roof is locally extremely thin, in some places there is no ependyma, and the roof consists of meninx only

9 The choroid plexus of the fourth ventricle absorbs colloiddally suspended particles from the internal cerebrospinal fluid

10 Interepithelial capillaries occur in the choroid plexus of the third ventricle, in the pineal tube and in the roof of the third ventricle

11 Transitions between meninx and connective tissue occur along the olfactory nerves, the optic chiasm, the trigeminal nerves and the first three cervical nerves

12 At these points the external cerebrospinal fluid drains into the connective tissue

13 With respect to trypan blue there exist a blood-cerebrospinal fluid barrier and a less absolute cerebrospinal fluid-parenchyma barrier With respect to india ink the second barrier is the stronger

Laboratory of Pathology, Oostersingel 63

# ELECTRICAL RESISTANCE OF THE SKIN

Effect of Size of Electrodes, Exercise and Cutaneous Hydration

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VARIOUS factors influencing the measurement of skin resistance have been repeatedly investigated. Various types of apparatus, electrodes and electrode pastes have been used in these investigations. Variations in skin resistance have often been observed which were not entirely understood. We have felt that by a better understanding of the variations in the technic of measuring skin resistance more consistent and comparable results could be obtained. The use of a standardized technic by different investigators would be helpful.

Several years ago we built an apparatus for measuring the galvanic skin response (psychogalvanic reflex). This apparatus made use of a Wheatstone bridge circuit, in which a pulsating, direct current of constant amperage flowed continuously through a subject who was connected into one of the arms of the bridge. Not long after we started to use this apparatus for investigating the galvanic skin response to auditory stimuli it was observed that it was sometimes difficult to obtain a constant resistance to be used as a base line from which the effect of a stimulus could be measured. As a rule the resistance dropped during the first twenty to thirty minutes, but it did not always drop the same amount. Other investigators<sup>1</sup> have also observed this drop. In addition, the apparent, or measured, resistance of the same area of skin on the same subject varied from day to day. It was not always possible to obtain a constant resistance even when all external stimuli were held at a minimum. What factors other than psychic stimuli were responsible for these changes in skin resistance?

A review of the literature and discussion of the problem with several investigators working in this field did not yield specific information as to the causes of change in apparent resistance other than psychic stimuli.

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1. Thouless, R. H. The Technique of Experimentation on the Psychogalvanic Reflex Phenomenon and the Phenomenon of Tarchanoff, *Brit. J. Psychol.* 20: 219-240 and 309-321, 1930.

Landis and DeWick<sup>2</sup> published a review of the entire field in 1929, which was extensively expanded by Landis in 1932.<sup>3</sup> Many reports by other investigators have appeared since then; the papers applying directly to the factors we are investigating will be cited in the context of the paper.

Our early work on this problem led us to believe that such factors as (a) variations in the size of the electrode, (b) the amount of activity previous to the measurement of the apparent resistance and (c) the hydration of the skin by the electrode paste had not been given sufficient consideration by many of the workers in this field. The results of the investigations of these three factors are reported in this paper.

#### APPARATUS

A simple apparatus was constructed for us by Dr. M. A. Wenger, making use of the Levine circuit.<sup>4</sup> The apparatus (fig. 1) consists of two 45 volt dry cells connected in series, two Centralab variable resistances of 50 and 750 ohms maximum resistance connected as a potential divider, a Triplet D C voltmeter no. 677 and a Triplet D C microammeter no. 676. The entire apparatus was assembled at a cost of less than \$25. Since the smallest scale division of the microammeter is 1 microampere, this instrument is not very accurate when one is working with extremely small currents. Up to the present we have been interested in large changes and have found this instrument sufficiently accurate for our needs.

#### FACTORS AFFECTING RESISTANCE OF SKIN

*Size of Electrode*—With any type of electrode the junction between the metallic element and the subject is always made with an aqueous solution of an electrolyte. Under some conditions this solution may be only the normal sweat on the skin. Inert nonelectrolytes, such as kaolin or agar, may be added to give a semisolid or gel consistency to the electrolyte solution. Some investigators have discussed the effect of the size of the electrode on the apparent resistance.

If the metallic element of the electrode is carefully placed on the skin, with only a film of the electrolyte solution between the metal and the skin, the area of the metallic element and the area of the skin wet with the solution are approximately equal. With certain types of electrodes, however, the metallic element may be at some distance from the skin, and the area of the metallic element may differ appreciably from

2 Landis, C. and DeWick, H. N. The Electrical Phenomena of the Skin (Psychogalvanic Reflex), *Psychol. Bull.* 26:64-119, 1929.

3 Landis, C. Electrical Phenomena of the Skin (Galvanic Skin Response), *Psychol. Bull.* 29:693-752, 1932.

4 Levine, M. Measurement of Electrical Skin Resistance. *Arch. Neurol. & Psychiat.* 29:828-842 (April) 1933.



the area of the skin wet with the solution. Under such conditions, how is the size of the electrode to be determined? If the area of skin wet with the electrolyte solution changes during the experiment as a result of evaporation of water from the electrode paste, how will this affect the apparent resistance of the skin? To answer these questions, the following investigations were carried out

A Lucite cup electrode<sup>5</sup> (fig 2), described in the following paragraph, was selected because it may be readily constructed in a variety of sizes, and the size of the metallic element within the Lucite cup may be varied independently of the size of the cup. The electrode paste is confined to a definite area of the skin, and evaporation of water from the paste is prevented. In addition, the electrode can be easily and quickly applied and removed from the cutaneous surface

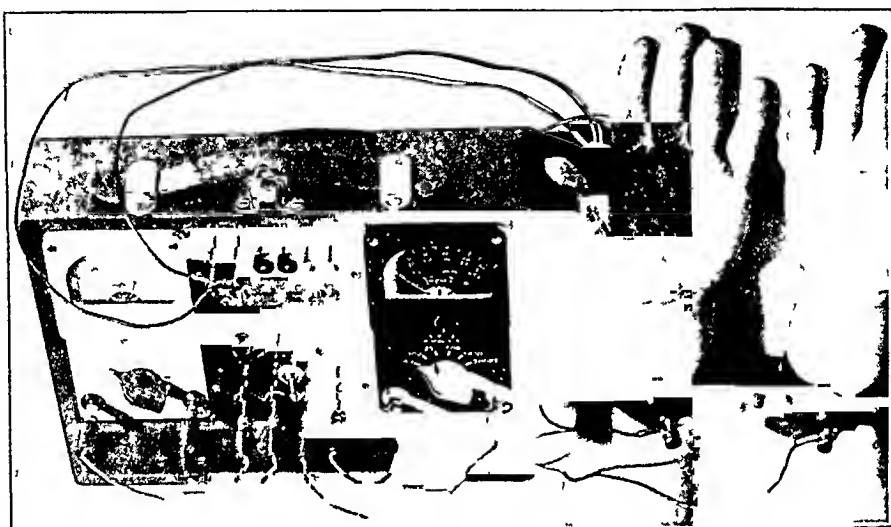


Fig 1—Apparatus for measurement of electrical skin resistance

The metallic element in this electrode is a thin (0.5 mm) zinc disk. The electrolyte solution is 1 per cent zinc sulfate made into a paste with 5 per cent agar. The electrode is constructed so that the zinc disk is in contact with the base of the shallow Lucite cup, 5 mm in depth. The disk has the same diameter as the cup, allowing only enough clearance so that it may be removed for cleaning. The cup is filled with the zinc sulfate-agar paste. The electrode is held in place on the skin by means of a strip of sheet rubber around the hand or arm. These electrodes may be quickly and easily applied to an extremity and held firmly in place with a minimum of discomfort to the subject.

Pairs of electrodes whose cups and disks were 1, 2 and 4 cm in diameter were constructed. The subject was lying down at rest during the entire experiment. Since it was desired to minimize the changes in resistance due to sweating, the volar surface of the forearm, which has fewer and less active sweat

<sup>5</sup> Designed by Dr. M. A. Wenger and manufactured by Forest Products, Inc., 739 Boylston Street, Boston.

glands than the palms, was chosen for this study. The skin of the volar surface of the forearm is anatomically similar to the skin of the dorsum of the hand, an area frequently used by other investigators.

A 2 cm electrode was placed on the midvolar surface of each forearm, and the apparent resistance was measured at a potential of 1 volt, the current being allowed to flow through the subject for not longer than three seconds. The electrodes were removed immediately after the reading was made, in this way the electrodes did not stay on the skin longer than one minute. This technic was used

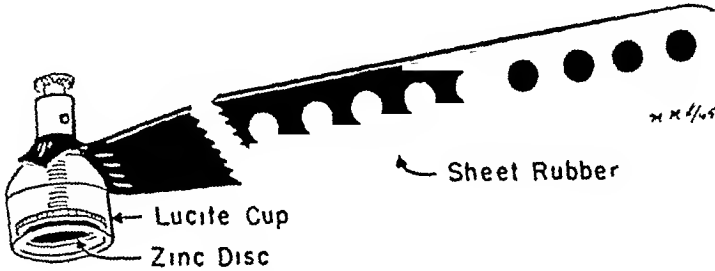


Fig 2—Lucite cup electrode

in order that any changes in the skin due to the flow of current or hydration of the skin might be minimized. Although one cannot be sure that no such changes occur in the skin, even when the current is allowed to flow for only a short time or when contact of the electrode with the skin is of short duration, evidence is available that if such changes do occur they are nearly reversible, and hence the four minute period allowed to elapse before the electrodes are again applied to the skin is ample time for recovery to take place.

For this experiment, measurements were made on the same area of skin every five minutes, until three or four successive measurements gave similar results. When the readings became constant, the subject was judged to be

TABLE 1—Effect of Size of Electrode on Apparent Skin Resistance\*

Size of Electrode		Apparent Resistance, in Ohms $\times 10^{-3}$ for Six Subjects					
Diameter, Cm	Area, Cm <sup>2</sup>	1	2	3	4	5	6
1.0	0.79	3,750	4,280	5,000	6,000	6,000	25,000
2.0	3.14	1,430	1,760	3,330	2,500	2,500	8,330
4.0	12.56	517	400	698	545	980	2,940

\* Voltage was 1.0

sufficiently rested, so that any previous activity he may have had no longer affected the skin resistance. This point was reached about thirty minutes after the subject lay down. After the thirty minute rest period a new area of the volar surface of each forearm closer to the antecubital space was chosen, and similar successive readings were made with pairs of electrodes which were 1, 2 and 4 cm in diameter. The apparent resistances determined for an experiment of this type on 6 subjects, in which the three sizes of electrodes were used, are shown in table 1. It is clearly seen in the values for each subject that the apparent resistance decreases as the size of the electrode increases.

If, in the circuit being investigated, the body of the subject conducted electricity in the same way as does an electrolyte solution, the current density (microamperes per square centimeters) would be constant and independent of the size of the electrode. In table 2, which shows the same data as table 1 calculated as current densities, it is seen that the current density is not constant when the size of the electrode changes. The greatest divergence occurs for the 1 cm electrodes. This

TABLE 2—*Variations in the Current Density\* as the Size of the Electrode Is Varied*

Size of Electrode		Current Density for SIX Subjects					
Diameter Cm	Area Cm <sup>2</sup>	1	2	3	4	5	6
1.0	0.79	1.01	0.89	0.77	0.63	0.64	0.25
2.0	3.14	0.69	0.54	0.39	0.38	0.38	0.19
4.0	12.56	0.46	0.60	0.34	0.44	0.26	0.14

\* Current density is expressed in microamperes per square centimeter

may be due to the lack of refinement in technic, or it may indicate the difference of the conductance of the body as compared with the conductance of an electrolyte solution. Nonuniformity of the skin no doubt affects these measurements.

When using other types of electrodes, we had the impression that the size of the metallic element could be varied appreciably without changing the apparent skin resistance as long as the area of skin wet with the electrolyte solution was held constant. The present type of electrode offered a good opportunity for studying this impression more

TABLE 3—*Effect of Changing the Size of the Metallic Disk Only on Apparent Skin Resistance\**

Area of Lucite Cup, Cm <sup>2</sup>	Area of Metallic Disk, Cm <sup>2</sup>	Apparent Resistance, in Ohms $\times 10^{-2}$ for SIX Subjects					
		1	2	3	4	5	6
12.56	12.56	833	517	400	3,070	6,230	
12.56	3.14	833	483	309	3,330	6,230	1,430
12.56	0.79	833	517	219	3,070	5,550	1,210

\* Voltage was 10

carefully. Measurements were made on the volar surface of the forearm of 6 subjects at rest for at least thirty minutes. The 4 cm cup was used with the 1, 2 and 4 cm zinc disks. Table 3 shows that the apparent skin resistance remained nearly constant if the area of skin wet with the electrolyte solution was constant, even when the area of the metallic element varied sixteenfold. The area of skin wet with the electrolyte solution will be called the "effective electrode."

The foregoing data indicate that care should be used in applying electrodes to the surface of the skin. If an area of the skin larger than the area of the electrode is accidentally wet with the electrolyte solution, the apparent skin resistance will be low, and as the wet area outside the electrode dries the apparent skin resistance will increase. This is specifically demonstrated in the following experiment.

Two sets of electrodes, each 2 cm in diameter, were applied to the volar surfaces of the forearms and allowed to remain on the skin continuously for the duration of the experiment. Measurements of resistance were made at a potential of 1 volt every five minutes until the resistances became constant. At this time an area about 1 cm wide outside each of two electrodes was wet by swabbing with a 1 per cent solution of zinc sulfate. The skin outside the other two electrodes was not wet with the solution.

The apparent resistance immediately decreased for the set of electrodes around which the skin was swabbed but as the skin spontaneously dried the apparent resistance gradually returned to almost the same value as that previous to swabbing. The apparent resistance remained constant for the unswabbed areas. Figure 3 also shows that the return after swabbing was hastened if the evaporation was speeded up by blowing the swabbed areas with air. Liu and Wu<sup>6</sup> referred to a decrease in resistance when they wet their electrodes with saline solution.

Thus it is clearly seen that the apparent resistance decreases as the size of the electrode is increased and that the size of the effective electrode is determined not by the size of the electrode itself, or of the metallic part of the electrode, but by the area of skin wet with the electrolyte solution. Although many investigators have pointed out the necessity of preventing evaporation from the electrode paste in order to avoid changes in the concentration of the paste, we believe that a greater artefact is due to changes in size of the effective electrode as evaporation occurs. Water or aqueous solutions are often used for cleansing the skin before the electrodes are applied, and subsequent evaporation of these solutions outside the area covered by the electrode changes the size of the effective electrode. The results of the experiment just described suggest that the changes in apparent resistance observed during profuse sweating, as in cases of hyperhidrosis, may be due to an increase in the size of the effective electrode when continuity is established between the electrode paste and the film of sweat outside the limits of the electrode. For an actively sweating palm the size of the effective electrode would be difficult to determine. In describing a technic for measuring skin resistance, the actual area of skin wet with the electrode solution should be stated, and this area should be held as nearly constant as possible for the duration of the experiment.

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<sup>6</sup> Liu, S. C., and Wu, H. A Method for Measuring the True Electrical Resistance of the Skin, with Some Observations, *Chinese J. Physiol.* **6** 63-70, 1932.

*Exercise*—Since measurements of skin resistance are frequently made on ambulatory subjects, the amount of activity just previous to the time when the resistance is measured will vary. Reports of these measurements do not always indicate the extent of this activity, such as walking or climbing stairs, and often do not state whether or not the subject was asked to rest before the measurement was made. During rest following exercise, there probably will be an increase in apparent resistance, possibly associated with decrease in sweating<sup>7</sup> and relaxation of muscular tension<sup>8</sup>. The following experiment has been chosen, from

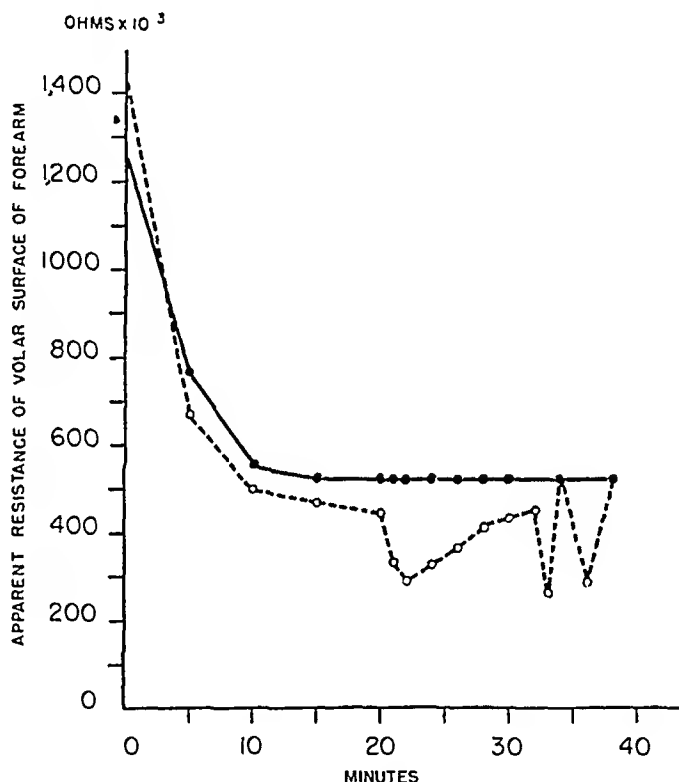


Fig 3—Effect on the apparent resistance of the skin of increasing the size of the effective electrodes by swabbing the skin around the electrodes

The solid line shows readings for the control electrodes, the broken line, readings for the electrodes around which the skin was swabbed with 1 per cent aqueous solution of zinc sulfate, at twenty, thirty-two and thirty-four minutes. Drying occurred spontaneously after the first swabbing, the area was blown with air after the second and third swabbings.

7 Richter, C P. Physiological Factors Involved in the Electrical Resistance of the Skin, *Am J Physiol* **88** 596-615, 1929

8 White, M M. Relation of Bodily Tension to Electrical Resistance, *J Exper Psychol* **13** 267-277, 1930. Wenger, M A. A Study of Physiological Factors. The Autonomic Nervous System and the Skeletal Musculature, *Human Biol* **14** 69-84, 1942

many similar tests we have made, to show the rise and fall of apparent resistance during rest and exercise

A subject who had been walking a little just previous to the experiment was asked to lie down. Lucite electrodes were immediately applied to the midvolar surfaces of both forearms and to both palms and were allowed to remain in place for the entire experiment. Single measurements of skin resistance at a potential of 1 volt were made on the forearms and the palms at five-minute intervals. For each measurement the current was allowed to flow for less than three seconds. After twenty minutes the successive measurements became relatively constant, indicating that the effect of any previous exercise had disappeared. After thirty minutes the subject was asked to stand up and start exercising by stepping up

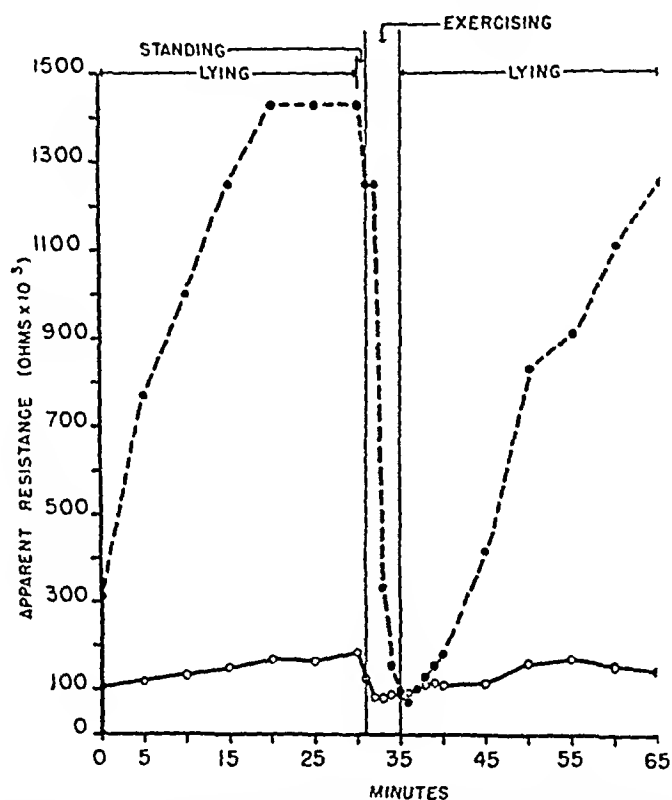


Fig 4—Effect of rest and exercise on the apparent resistance of the skin. The solid line indicates readings for the palms, the broken line, readings for the volar surfaces of the forearms.

and down on a 12 inch (30 cm) step at the rate of sixteen times per minute. This was continued for four minutes, measurements of resistance being made every minute. The subject again lay down, and measurements of resistance were continued every five minutes for thirty minutes. The results of this experiment are shown in figure 4.

During the first twenty minutes the apparent resistance of both the forearms and the palms rises. We believe that the change in apparent resistance during the first rest period is the resultant of at least two factors: the rise in resistance resulting from resting and a decrease in resistance associated with hydration of the stratum corneum by the electrode paste. The latter factor will be discussed in the succeeding section of this paper.

The apparent resistance of the volar surface rises fairly uniformly. This probably indicates that the sweat glands of this surface steadily decrease their rate of functioning. The lower apparent resistance of the palms as compared with that of the volar surfaces at the end of the rest period probably indicates that during rest the sweat glands of the palms are more active than the sweat glands of the forearms. As the subject begins to exercise, the palmar resistance quickly drops to a minimum, at about which level it remains during continued exercise. The resistance of the skin of the forearm drops more slowly but reaches approximately the same level. We feel that this low level of resistance of both the palms and the volar surfaces of the forearms represents the resistance of these areas of skin at a time when the sweat glands are actively functioning. It is interesting that at this time the apparent resistance of the palms and that of the surfaces of the forearms are of the same magnitude. During the rest period following exercise the rise in apparent resistance, which accompanies resting, with its diminished activity of the sweat glands, is again seen.

This experiment indicates that a subject for measurements of skin resistance should have a rest period before the measurements are made in order to minimize the effects of his previous activities.

*Hydration of the Skin*.—In a study of some of the factors associated with the measurement of skin resistance, Levine<sup>4</sup> stated

One might expect that the paste, soaking the skin, might lower its resistance, or that the paste might provide stimuli which could produce changes. But again the fact that after long periods of contact with the paste, the resistance may, in different patients, remain the same, may increase or may decrease, offers strong evidence against the idea that the paste itself can change skin resistance.

We, too, have observed that during the first half-hour the electrodes are on the skin the apparent resistance may sometimes decrease, sometimes increase or sometimes remain nearly constant. These variations, which may be large or small, may occur in the same subject when measurements are being made at different times or may be observed on two subjects measured at the same time. We have not felt, however, that these observations justified the conclusion drawn by Levine that this is "strong evidence against the idea that the paste itself can change skin resistance." The electrode paste might be acting on the skin so as always to change the apparent skin resistance in one direction. If at the same time another factor were acting to change the skin resistance in the opposite direction, the resultant change in resistance would be the sum of the changes caused by the two factors, and the resultant change might be in either direction, depending on which factor was the greater.

We believe that this is actually what was happening in the experiments of Levine, and what happens when many types of electrodes are used. In the previous section of this paper it was shown that the

apparent skin resistance increases during a period of rest following exercise. We believe that the electrode paste causes hydration of the outermost layer of the skin, which results in a decrease in apparent skin resistance. Ebbecke<sup>9</sup> has referred to this drop in resistance which accompanies hydration of the skin. If the changes due to resting and to hydration occur simultaneously, the resultant change is the algebraic sum of these two factors and may be either an increase or a decrease, depending on which factor is the greater. The following experiments were devised to test this hypothesis and to evaluate the factors of exercise and hydration.

Subjects were asked to lie down at the beginning of the experiment and remained lying down with their arms in the same position throughout the experiment. Two of the cup electrodes 2 cm in diameter, filled with a 1 per cent zinc sulfate-agar jelly, as previously described, were placed on the volar surface of each forearm near the antecubital space. These electrodes were allowed to remain in position on each forearm in contact with the skin throughout the whole experiment, which lasted about one hour. Another set of similar electrodes was placed on the forearms about 3 cm below the first set. During the first part of the experiment the second set of electrodes was allowed to remain on the skin each time only long enough to obtain a reading and then removed. The time required to obtain a reading was from thirty to sixty seconds, and the actual time during which current flowed through the skin was less than three seconds. A potential of 4 volts was used, and readings were made at five minute intervals. After each reading the electrodes were removed, and the areas of skin in contact with the electrodes were gently wiped with gauze. After the apparent resistance became constant, i. e., when three consecutive readings were the same, it was judged that the factor of exercise, or, more correctly, that of rest following exercise, was no longer causing the apparent skin resistance to change. At this point the electrodes were placed on the same areas of the skin and from this time on were not removed after each reading.

Figure 5 shows the changes which occurred in similar experiments on 2 subjects. The solid line in each graph indicates changes as measured with the electrodes which remained in place continuously throughout the whole experiment. The dotted line in each graph represents the changes as measured with electrodes which were removed after each reading for the first thirty minutes and then allowed to remain continuously on the skin for the second thirty minutes. We believe that when the electrodes were removed the changes in resistance were due primarily to the rest following exercise. When the electrodes subsequently remained in place, the changes were due primarily to the hydration of the skin by the electrode paste. As shown in figure 5 *A*, the hydration caused a drop in apparent skin resistance which was greater than the rise which occurred during resting. Thus there resulted a net

<sup>9</sup> Ebbecke, U. Die lokale galvanische Reaktion der Haut, Arch f d ges Physiol **190** 230-269, 1921



decrease in apparent skin resistance. In figure 5 *B* the drop caused by the hydration is less than the rise caused by resting, and hence there is a net increase in the apparent resistance. The results for these 2 experiments are shown because for 1 of the subjects the apparent resistance rose and for the other the resistance fell during similar determinations. This is the situation mentioned by Levine.

The skin is a complex organ, anatomically and physiologically. When a 1 per cent zinc sulfate-agar jelly is placed on the skin, many changes

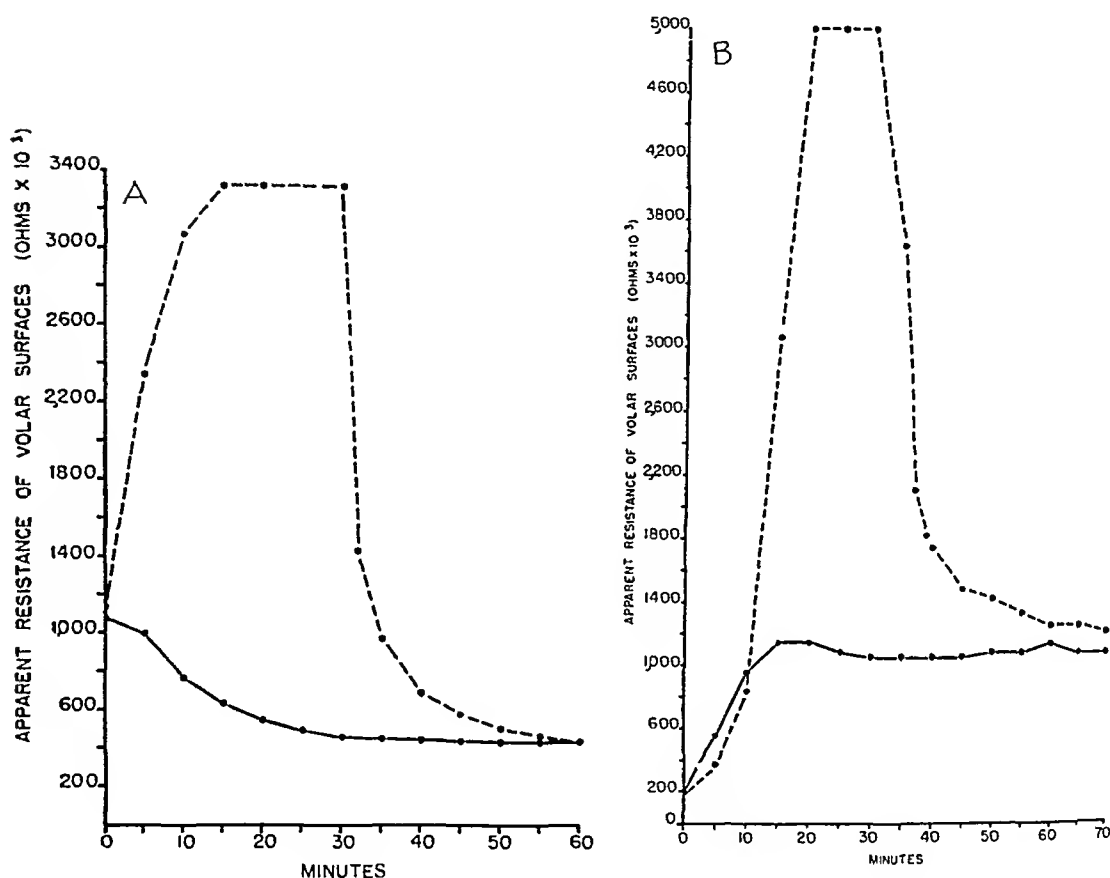


Fig 5—Effect on the apparent resistance of the skin of removing electrodes between readings. The broken line indicates readings for the first set of electrodes, removed between readings for thirty minutes and then left on the skin continuously, the solid line, readings for the second set of electrodes, left on the skin continuously. The graphs are for 2 subjects, *A* and *B*.

may occur which might cause a drop in skin resistance. It is our opinion that one of the most probable mechanisms producing this change is the hydration of the outermost layer of the skin, the stratum corneum. Most of the tissues of the body are relatively good conductors of electricity. The skin, on the other hand, is a poor conductor, i. e., it has a high resistance. The seat of this high resistance is probably the outer layer

or layers of the skin, since the resistance can be greatly reduced by the most superficial abrasion or puncture<sup>10</sup> The stratum corneum is thought to contain less than 20 per cent water, as compared with the deeper layers of skin and other body tissues, which contain from 75 to 80 per cent water<sup>11</sup> The cells of the stratum corneum have lost their water during the normal process of keratinization These cells, however, relatively easily take up water again, i. e., become hydrated On hydration the stratum corneum might be expected to become a better conductor, since electrolytes are already present in this tissue If this hypothesis is correct, the skin when covered with a gauze compress soaked with distilled water should show a drop in resistance similar to that occurring when it is covered with an electrode of the type previously described Also, the resistance should again rise when the skin is allowed to dry out by removing the electrodes from a hydrated area The results of the following experiment, as shown in figure 6, support this hypothesis

Two sets of electrodes were placed on the forearms, as in the previous experiment During the first thirty minutes of rest each set remained on the skin only long enough to obtain one measurement every five minutes After thirty minutes one set of electrodes was placed on the skin and allowed to remain in place, and the current was allowed to flow through the skin for only three seconds each time the resistance was measured The other areas of skin the resistance of which had been measured were covered with gauze compresses wet with distilled water The area of each compress was the same as that of the electrodes These remained on the skin for fifteen minutes At the end of this time the compresses were removed, the areas gently but thoroughly dried with gauze and the electrodes immediately placed on the skin and allowed to remain in contact with the skin for fifteen minutes After fifteen minutes the electrodes were again removed and during the succeeding twenty minutes were placed on the skin only long enough to make a measurement of resistance once every five minutes

In figure 6 it is seen that the area to which no compress was applied shows a change in apparent resistance quite similar to that illustrated by the broken lines in figure 5 It is also seen that the areas wet with distilled water alone, as illustrated by the solid line in figure 6, show a decrease in apparent resistance during the fifteen minute period of application of compresses approximately equal to the decrease in apparent resistance which occurs when the electrodes are held continuously to the skin

10 Richter, C. P. The Significance of Changes in the Electrical Resistance of the Body During Sleep, *Proc Nat Acad Sc* **12**:214-222, 1926 Lewis, T., and Zotterman, Y. Vascular Reactions of the Skin to Injury VIII The Resistance of Human Skin to Constant Currents in Relation to Injury and Vascular Response, *J Physiol* **62** 280-288, 1927 Densham, H. B., and Wells, H. M. The Mechanism by Which the Electrical Resistance of the Skin Is Altered, *Quart J Exper Physiol* **18** 175-184, 1927

11 Rothman, S., and Schaaff, F., in Jadassohn, J. *Handbuch der Haut- und Geschlechtskrankheiten*, Berlin, Julius Springer, 1929, pp 167-171 and 275-278

When the electrodes are removed from the skin, the apparent resistance again increases, a change which we feel is due to drying out of the stratum corneum

These experiments show that the apparent resistance drops as a result of contact of water or aqueous solutions with the skin and that this decrease is caused by hydration resulting from contact of the electrode paste with the skin. In experiments which measure the effect of various stimuli on apparent resistance, it would be best to allow this

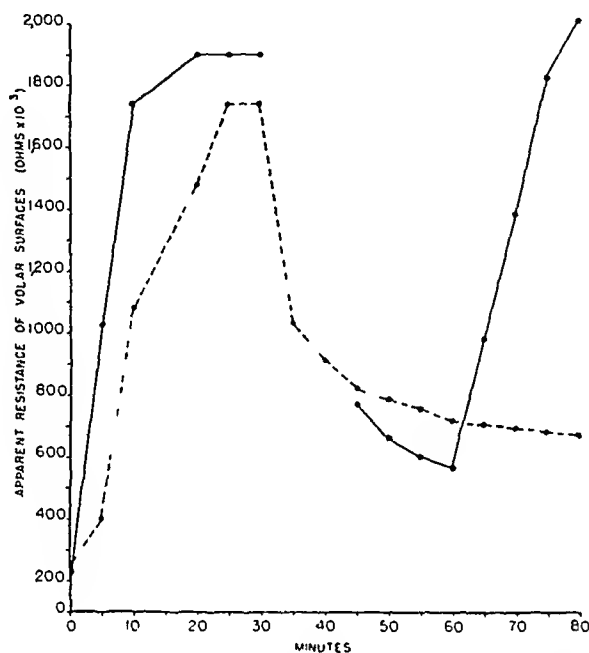


Fig 6—Effect on the apparent resistance of the skin of application to the skin of compresses wet with distilled water. The broken line indicates readings for the first set of electrodes, removed between readings for thirty minutes and then left on the skin continuously for fifty minutes. The solid line represents readings for the second set of electrodes. These electrodes were removed between readings for thirty minutes, compresses were applied for fifteen minutes, and electrodes were left continuously on the skin for fifteen minutes and then removed between readings during the final twenty minutes.

hydration to occur and the apparent resistance to become constant before attempting to measure the effect of the stimuli.

#### SUMMARY

The following observations were made: 1. Apparent skin resistance decreases (*a*) as the size of the electrode is increased and (*b*) as the superficial layer or layers of skin become hydrated as a result of continuous contact of electrode paste with the skin. 2. Apparent skin resistance increases during rest following exercise or activity. 3. The size of the electrode is determined by the area of skin wet with the

electrode paste or sweat (effective electrode), and not by the absolute size of any part of the electrode itself. 4 Any aqueous film, such as sweat, outside the area of the electrode, but continuous with the electrode paste, acts to increase the size of the effective electrode. 5 The values for apparent resistance of two areas of skin, such as the palmar and the volar surface of the forearms which may differ greatly when the subject is at rest approach the same magnitude when the patient exercises vigorously.

In any experiment in which the effect of a stimulus on apparent skin resistance is being measured one should be sure that the resistance is not changing as a result of (a) variation in the area of skin wet with the electrode paste or with sweat, (b) rest following exercise or (c) hydration of the skin by the electrode paste.

## NEUROLOGIC DISEASE FOLLOWING INFECTIONS OF THROAT AND SKIN AND INCIDENCE OF DIPHThERITIC INFECTIONS

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MEDICAL CORPS, ARMY OF THE UNITED STATES

A NEUROLOGIC syndrome apparently infectious in origin has been reported among the members of the armed forces of the United States in the recent war. These patients have shown varying degrees of neurologic disturbance, ranging from mild peripheral neuritis to severe debility involving the central nervous system as well as the peripheral nerves, similar to the Guillain-Barre syndrome<sup>1</sup>. The great majority of these patients had, or had previously had, cutaneous disease. Those with no history of cutaneous disease gave a history of a severe sore throat during the period of approximately one month prior to the onset of neurologic symptoms.

It has been assumed by some investigators<sup>2</sup> that the disorder in these patients was the result of infection with *Corynebacterium diphtheriae*. In support of this view, virulent diphtheria organisms have been isolated from the throat, nose and lesions of the skin of some of the patients. In the majority of instances, however, cultures have failed to show *C. diphtheriae*. It is, of course, known that the earlier in the disease a culture is obtained, the greater is the likelihood of a positive culture for *C. diphtheriae* if that is the organism concerned. There is some evidence, also, that diphtheria organisms may lose their virulence while still present in the human body. It is not the purpose of this paper to prove or disprove the theory that neurologic syndromes following cutaneous disease are the result of exposure to the toxin of the diphtheria bacillus. In all likelihood some are of diphtheritic origin. There is, however, considerable reason to doubt that *C. diphtheriae* is the sole etiologic agent, and the results of certain studies will be offered which seem to support the possibility that other factors may be concerned.

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1 Roseman, E, and Aring, C D. Infectious Polyneuritis - Infectious Neuritis, Acute Polyneuritis with Facial Diplegia, Guillain-Barre Syndrome, Landry's Paralysis, etc, *Medicine* **20** 463, 1941.

2 Liebow, A A, MacLean, P D, Bumstead, J H, and Welt, L G. Tropical Ulcers and Cutaneous Diphtheria, to be published. Norris, R F, Kern, R A, Schenck, H P and Silcox, L E. Diphtheria in the Tropics. A Report of Eighteen Cases on a United States Naval Hospital Ship, *U S Nav M Bull* **42** 518, 1944.

Two series of patients will be considered. The first series was studied in the late winter and spring of 1943, when I was assigned to a general hospital in Melbourne, Australia.<sup>3</sup> It consisted of 13 members of the first Marine division, which was staging there at the conclusion of the campaign at Guadalcanal. These men had been in action for varying periods between early August and late December 1942. Some had been present at the initial landing, when food and medical supplies had been inadequate. Others had arrived late in the campaign, when supplies and food were relatively good. One patient was a member of a headquarters company, arriving late in the campaign, and had been on the island only forty days prior to evacuation.

TABLE 1—Data on Group of Patients Studied in Melbourne, Australia, in 1943

Case No	Date of Arrival on Guadalcanal	Development of Sore Throat	Interval in Days Between		Classification as to Severity†	Cutaneous Ulcers	Total Spinal Fluid Protein, Mg per 100 Cc	Presence of Antibodies to Diphtheria Toxin
			Sore Throat and Onset of Neuritis	Onset of Neuritis and Maximum Involvement				
1	Aug 7	Dec 15	7	74	B	Yes	† Pandey	No
2	Aug 7	Dec 1*	30	36	B	Yes	38	Yes
3	Aug 7	Nov 30	3	23	A	Yes	52	Yes
4	Aug 21	Nov 15	15	65	B	No	42	Yes
5	Aug 21	Nov 5	25	73	B	Yes	92	No
6	Sept 17	Oct 15	10	114	C	Yes	66	No
7	Sept 18	Nov 15	45	24	B	No	100	
8	Sept 18	Dec 1	60	25	C	Yes	197	Yes
9	Sept 18	Nov 23	14	29	C	Yes	82	No
10	Sept 18	Oct 15	10	136	A	No	30	Yes
11	Nov 11	Nov 20	30	61	C	No	101	No
12	Nov 11	Dec 15	30	39	B	Yes	217	Yes
13	Nov 12	Dec 25	37	62	C	No	39	No

\* The patient had had a moderately severe febrile illness but no sore throat.

† For the meaning of A, B and C see explanation in the text.

He had never been on a jungle patrol, his diet was adequate, and his living conditions were relatively good.

There was little, if any, close contact between the Marines and the natives, as most of the latter had taken to the jungle with the onset of the fighting. Contact with Japanese was limited to hand to hand combat and burial details. All had bathed in and drunk from the Lunga River and its tributaries. This is a sluggish tropical stream and almost certainly contaminated.

With 1 exception every member of this group gave a history of a severe sore throat from three to sixty days prior to development of any neurologic symptoms or signs. Eight of the 13 patients also gave a history of "sores" on the lower part of the legs and the feet during the campaign. The Marine without a history of sore throat had had an

<sup>3</sup> These studies were carried out under the direction of Lieut Col Edward O Harper, Medical Corps, Army of the United States.

unexplained febrile illness thirty days prior to neurologic changes and was one of those with ulcers of the skin

The data on these patients are summarized in table 1. Column 2 of the table shows the date of the patient's arrival on Guadalcanal. Five of the group arrived in August, 5 in September and 3 in November. Column 3 shows the date of onset of sore throat. There is no correlation between the time of arrival and the date of development of the sore throat except that no sore throats occurred prior to arrival on Guadalcanal. Column 4 gives the number of days elapsing between development of the sore throat and the onset of neurologic signs and symptoms. It is apparent that this is one of the most variable points in this series, and its variability is one of the most difficult to explain. Column 5 shows the number of days required for the neurologic disease to reach its maximum severity, and column 6 indicates the severity of the disease. Classification A included patients whose disease was mild, with merely evidence of involvement of peripheral nerves, mild sensory changes and loss of the deep reflexes. Classification B is one of medium severity. The patients, in this category, in addition to signs of involvement of peripheral nerves, also gave evidence of damage to cranial nerves and lesions of the spinal cord. They were likely to have a history of motor weakness, in spite of which they were never seriously incapacitated. In classification C in which all the patients showed evidence of severe neurologic disease, signs referable to the cranial nerves were conspicuous. These patients had pronounced weakness to complete paralysis of the extremities and marked ataxia. Two patients fell into classification A, 6 into classification B and 5 into classification C. It is apparent that the severity of the disorder bore little, if any, relation to the time required for the disease to reach its maximum. The time for the patients in classification A varied from twenty-three days to one hundred and thirty-six days, that for patients in classification B, from twenty-five to seventy-five days, and that for patients in classification C, from twenty-five to one hundred and fourteen days. Column 9 shows the results of studies on the serum of 12 of these 13 Marines for the presence of diphtheria antibodies. Six of them had demonstrable antibodies, and 6 had no antibodies. Column 8 shows the maximum protein levels of the spinal fluid for these patients. It is apparent that there is not much relation between the severity of the disease and the total protein of the spinal fluid. With 1 exception, only single determinations were made and it is possible that the correlation might have been better if the result of repeated taps over the entire course of the disease had been used.

Twelve of 13 patients were studied to determine whether their serum contained any antibodies against the diphtheria toxin. The Jensen

modification of the Romer test was employed<sup>4</sup> Serums of these 12 patients were inactivated at 56 C for fifteen minutes and then mixed in equal volumes with diluted diphtheria toxin Two dilutions of toxin were used—one equal to twice the Schick test dose and the other to ten times the Schick test dose The mixtures were then injected intradermally into the skin of 2 rabbits Serums from 13 control patients, who were carefully questioned as to any previous history of sore throat or neurologic complaints, were treated in a similar fashion The results of this procedure are shown in table 2 As is shown there, the serums of both the neurologic and the control group neutralized diphtheria toxin to approximately the same extent The serum of only 1 patient was able to neutralize the higher dilution, but it failed to neutralize the lower dilution

One patient (13, table 1) was treated for severe sore throat, which had developed approximately three weeks prior to his admission to the hospital On his admission cultures showed hemolytic streptococci No diphtheria bacilli were found on repeated cultures. He had typical

TABLE 2—Results of Titration of Serum Antitoxin

	Total Number	Positive Schick Reaction $\times 2^*$	Positive Schick Reaction $\times 10^*$
Melbourne patients with neuritis	12	5	6
Melbourne controls	13	6	6

\* Two dilutions of diphtheria toxin were used one equal to twice the Schick test dose and the other to ten times the Schick test dose

acute glomerulonephritis shortly after his admission Thirty-seven days after the onset of his sore throat he manifested early neurologic changes, which gradually progressed to the point that he was unable to get out of bed Titration of his serum on the skin of a rabbit failed to show any antibodies to diphtheria toxin

It was felt, on the basis of this evidence, that in this particular group of patients the neurologic syndromes were nondiphtheritic in origin A filtrable virus as the etiologic agent in a neurologic syndrome of this type has long been considered by some investigators<sup>5</sup> An effort was made to isolate a possible virus agent by injecting pooled washings from the nose and throat and serums into the amniotic cavity of 12 day chick embryos, after the method of Burnet<sup>6</sup> Spinal fluid was injected

4 Jensen, C Die intrakutane Kaninchenmethode zur Auswertung von Diphtherie-Toxin und Antitoxin, *Acta path et microbiol Scandinav*, 1933, supp 14, p 1 Romer, P H Ueber den Nachweis sehr kleiner Mengen des Diphtheriegiftes, *Ztschr f Immunitatsforsch u exper Therap* **3** 208, 1909

5 Bradford, J R, Bashford, E D, and Wilson, J A Acute Infectious Polyneuritis, *Quart J Med* **12** 88, 1919

6 Burnet, F M Influenza Virus Infections of Chick Embryo Lung, *Brit J Exper Path* **21** 147, 1940



intracerebrally into Swiss mice Stool emulsions, mixed with ether and left overnight at a temperature of 4 C., were injected intraperitoneally into monkeys All these attempts to isolate a virus were complete failures—the embryos showed no changes, and all the test animals exhibited no ill effects

It is unfortunate that it was not possible to follow these patients to complete recovery For military reasons it was necessary to evacuate them to the United States as soon as they were able to travel All

TABLE 3—Data on Group of Patients Studied at Moore General Hospital in 1945

Type of Disease	Number of Patients	Average Interval in Days from				Schick Tests, per Cent Positive Reac- tions	Classification as to Severity *			Average Total Protein of Cerebro spinal Fluid, Mgr per 100 Cc
		Initial Cuta- neous Disease to Open Skin Disease	Open Skin Disease to Neuritis	Onset of Neuritis to Maximal Severity			A	B	O	
Primary ulcers	17		91	45	35	2	6	9	83	
Secondary ulcers	19	113	85	47	35	6	7	6	95	
No ulcers	9	91	81	45	33	4	2	3	95	
Cutaneous diphtheria	5	156	115	45	80	1	3	1	60	

\* For the meaning of classifications A, B and O see explanation in text

TABLE 4—Data on Group of Ten Patients Who Had Severe Sore Throat During Course of Cutaneous Disease and Prior to Onset of Neurologic Symptoms

Type of Disease	Number of Patients	Average Interval in Days Between				Schick Tests, per Cent Positive Reac- tions	Classification as to Severity (See Text)			Average Total Protein of Cerebro spinal Fluid, Mg per 100 Cc
		Sore Throat and Neuritis	Open Cutaneous Disease and Neuritis	Onset of Neuritis to Maximum Severity	A		B	C		
Proved faucial diph- theria	2*	29	52	52	50	0	1	1	72	
Probable faucial diphtheria, viru- lence tests not done	5	23	69	51	20	1	2	2	89	
Severe sore throats but not diphtheria	3	42	93	57	67	1	0	2	57	

\* One patient also had virulent organisms in the skin

showed definite improvement before evacuation was requested It was estimated that the total duration of the neurologic syndrome from onset to complete recovery in this group of patients averaged seven months, with a minimum of five months and a maximum of eight months Most of this group had one or more malarial relapses during the course of their neurologic disease Only 1 patient showed a questionable exacerbation of his neurologic signs None of them showed any apparent neurologic symptoms as a result of antimalarial treatment—in this case

a quinine, quinacrine (atabine) and pemaquine naphthoate (Plasmo-chin) routine

The second group of patients, totaling 60, were at Moore General Hospital, Swannanoa, N. C., during the last three months of 1944 and the first nine months of 1945. They had all been evacuated from the Pacific theaters because of cutaneous disease. These data on these patients are summarized in tables 3 and 4. Table 3 deals with the 50 patients who gave no history of having had a sore throat. Of these, 17 patients had a history of "tropical ulcers" as the first manifestation of any disease of the skin. Nineteen stated that their tropical sores followed other types of cutaneous disease, including epidermophytosis, infectious eczematoid dermatitis and atypical lichen planus. Nine patients stated that they had never had any ulcers but did admit that their cutaneous lesions had on occasion been weeping or had been secondarily excoriated. There were 5 patients, or 10 per cent—4 with tropical ulcers and 1 with an eczematoid type of atypical lichen planus—cultures of whose skin were positive for *C. diphtheriae*.

It is evident from examining table 3 that the patients for whom positive cultures for diphtheria organisms were obtained had had cutaneous disease for a longer time than had the other three subgroups. The interval between the development of the open lesions and the onset of the neuritis was also somewhat greater on the average. Four of the 5 patients with proved diphtheritic neuritis had positive reactions to the Schick test at the time the cultures were positive, whereas for those patients from whom diphtheria organisms could not be obtained the reaction to the Schick test was positive in 35 per cent.

The patients were classified as to the severity of the neurologic disease by a scheme similar to that for the Melbourne group. The patients with primary ulcer had a higher percentage with disease of grade C severity than had any of the others. The last column in table 3 shows the average total protein of the spinal fluid for the four subgroups. The figure for the group with cutaneous diphtheria is considerably less than that for the others.

Table 4 summarizes the data on the 10 patients who in the course of their disease and prior to the onset of neuritis had severe sore throats. Of these, 2 had proved faucial diphtheria (1 of these patients also had virulent corynebacteria in the skin), 5 had probable diphtheria—on these no tests for virulence had been made—and 3 had sore throats from which no diphtheria bacilli could be isolated. Only the aforementioned patient had virulent organisms in the skin, and all the patients fell into the classification of "secondary ulcer" or of "no ulcer." Both patients with faucial diphtheria had received diphtheria antitoxin. Three months later 1 had a positive reaction to the Schick test and the other a negative reaction. Of the 5 patients with "probable diphtheria," none

of whom received antitoxin, only 1 gave a positive reaction to the Schick test. The classification into groups A, B and C and the results of determinations of the spinal fluid protein require no comment.

The results of Schick tests on this group are shown in table 5. When the 5 patients with proved cutaneous diphtheria and the 2 patients with proved faucial diphtheria are omitted, it is seen that the percentage of positive reactions is essentially the same as that for the control group. The control group here was obtained by analyzing the results of all Schick tests on male enlisted personnel, exclusive of this study group. If the 5 patients with "probable" faucial diphtheria had been excluded also, the percentage of positive reactions would have been slightly higher, inasmuch as 4 out of these 5 patients gave a negative reaction to the Schick test dose of toxin.

It is admitted, of course, that results of the Schick test, particularly in an adult group, are not entirely conclusive. Certainly, the presence of a positive reaction to the Schick test in a single patient would be of little or no significance, but it is also felt that in as large a group as

TABLE 5—Results of Schick Test

		Positive Reactions to Schick Test	
		Number	Per Cent
Moore	Patients with neuritis at General Hos		
pital		54	35
Moore	General hospital controls	272	99

this one there should be some decrease in the percentage of positive Schick reactions if this neurologic syndrome were due to diphtheria.

Two interesting cases will be reported briefly. The first patient had the primary ulcers when he was on Leyte. Three weeks after their onset, while a patient in a general hospital, he suddenly experienced vertigo, deafness in the right ear and diplopia. These were followed by rapidly progressing weakness and loss of sensation in the extremities. He was evacuated to the United States and was admitted to one of the wards for diseases of the skin at Moore General Hospital. On admission his skin had cleared, but he showed the characteristic neurologic changes of the severe form (classification C) of this syndrome. His spinal fluid protein was over 100 mg per hundred cubic centimeters, and his reaction to the Schick test was positive. Approximately one month later, and a total of two months after the onset of neurologic signs and symptoms, typical faucial diphtheria developed. This responded satisfactorily to antitoxin, and the Schick reaction became negative. It is reasonable to believe that had this man's neurologic symptoms been the result of the action of diphtheria toxin he should have shown some immunity—instead he was not immune and contracted diphtheria.

The second patient had been hospitalized for atypical lichen planus and had been evacuated to the United States. Approximately one month after arrival there he was ready for furlough. He awakened one morning and found that he had trouble in accommodating. In the next forty-eight hours severe weakness developed, and in a week he was bedridden, with complete quadriplegia. His spinal fluid protein was nearly 200 mg per hundred cubic centimeters. This patient had not had a sore throat, nor had he had tropical ulcers. He did state that at one time the papules of lichen planus had been somewhat excoriated. This patient remained completely incapacitated for thirty-six days, before recovery set in.

#### SUMMARY

Two series of patients with a syndrome showing various degrees of involvement of the nervous system are presented. All but 1 of the first series had as a precursor to the neurologic changes a severe sore throat. This 1 patient complained of a febrile illness thirty days prior to any neurologic complaint. Eight of the 13 patients also had had "tropical ulcers" while on Guadalcanal. The sore throats as described were extremely severe and incapacitating for a matter of weeks. At the time that these patients were hospitalized in Melbourne, intensive investigation, with the cooperation of the medical officers of the United States Navy attached to the Marine Corps, failed to disclose anything suggesting that these patients had had diphtheria. There had been no reports of diphtheria on Guadalcanal so far as the medical officers stationed there were aware. There had been numerous patients with severe sore throat, and many of these had been studied for possible diphtheria, with completely negative results. If these patients had had diphtheria of this degree of severity, some deaths would have been expected, inasmuch as no antitoxin was administered. On the basis of the clinical study, the Schick test and the titration of diphtheria antitoxin in the serum, it was believed that the neurologic syndrome in this series of patients was not postdiphtheritic.

The second series, of 60 patients was studied at Moore General Hospital about two years later. In this series, 2 had proved cases of faucial diphtheria and 5 proved cases of cutaneous diphtheria. There were 5 others who probably had had faucial diphtheria but from whose cutaneous lesions *Corynebacteria* had never been isolated. The majority of the group showed no evidence of either faucial or cutaneous diphtheria but exhibited a neurologic syndrome which seemed to be the sequela of severe cutaneous disease.

The neurologic changes varied in severity, sometimes resulting in temporary complete paralysis of the limbs but ending in complete recovery in all cases which we were able to follow to completion. Whereas clinically this observation is not inconsistent with the neurologic

changes seen after diphtheria, it is felt that the evidence presented indicates that *C diphtheriae* was not the causative agent of the neurologic syndrome in most of these patients

#### CONCLUSIONS

1 Thirteen patients with a postinfectious neurologic syndrome were studied in the Fourth General Hospital in Australia in 1943. Attempts to isolate a filtrable virus were unsuccessful. There was no evidence to suggest that the condition of any of these patients was the result of diphtheritic infection.

2 Sixty patients with a similar disturbance were studied at Moore General Hospital in 1945. Of these, the neurologic syndrome followed proved cutaneous diphtheria in 5, proved faucial diphtheria in 2 and severe sore throat which was probably diphtheritic in 5 others. There was no evidence to suggest that diphtheritic infection had played any part in the disease of the remaining 48 patients.

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# INTRAVENOUS INJECTION OF SODIUM AMYTAL AS A TEST FOR LATENT ANXIETY

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**S**ODIUM amytal has been widely utilized in the investigation and treatment of mental disorders. Its effectiveness in probing and clarifying stuporous psychotic states and its value in alleviating major hysteria are examples of its usefulness, which find expression in the routine daily work of most psychiatrists. There is, however, an area in the field of psychiatry where sodium amytal has been little used, yet an area where its utilization may prove fruitful indeed. This encompasses the so-called anxiety or tension states, by far the largest category of the psychoneuroses.

The bulk of the conditions included under the clinical label of "psychoneurosis" cannot be adequately designated by such descriptively specific diagnoses as conversion hysteria, obsessive-compulsive states and hypochondriasis. Rather, they must be grouped together on the basis of the broad concept of tension engendered by frustration, thwarting and insecurity, and are consequently best and most simply described as the tension, or anxiety, states. The pattern of anxiety which the organism may display are diverse, but they can be demarcated and the symptoms of each pattern itemized. One such pattern, for example, may be tension expressing itself through the gastrointestinal tract. Another constellation of symptoms may be derived chiefly from the musculoskeletal system.

Among the musculoskeletal symptoms of anxiety in an individual patient one might find feelings of "drawing" in the temples, eyes and neck, severe occipital headaches, a feeling of unsteadiness while walking, and easy fatigability. This pattern of symptoms is not uncommon, is readily diagnosed as an anxiety state and is recognized as requiring psychotherapy.

Anxiety or tension symptoms, however, are not always readily recognized as such. When they appear in unusual constellations, or when isolated symptoms appear in patients not considered previously psycho-

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neurotic, the origin of the complaints may be in doubt. Any individual anxiety symptom may therefore so closely resemble a symptom produced by a truly organic process that differentiation by the usual diagnostic tests may be impossible. So far as the patient's verbalization of his complaint is concerned, there is no significant difference between that of functional and that of organic origin. Nor, indeed, in the patient's awareness is there a difference. The headache resulting from tension in the muscles of the forehead and temples caused by anxiety seems as severe and as incapacitating as the headache produced by increased intracranial pressure. The nausea which accompanies the gastrointestinal pattern of anxiety is as real and sickening to the sufferer as the nausea of intestinal obstruction.

When it proves impossible to determine the existence of an organic basis for the patient's complaint, the physician may turn slowly to the concept of psychoneurotic causation. In most instances, however, the diagnosis of psychoneurosis is one evolved by the exclusion of every potential somatic cause, no matter how remote the likelihood of its presence. This process is often slow, costly and, in the end, unrewarding. We feel that it is possible to prove the "nonorganic" origin of many symptoms by a concrete diagnostic test. The test consists in the intravenous administration of small amounts of sodium amytal, injected fairly rapidly. Within one to five minutes, in most cases, the patient will note a definite abatement of his complaint if it is truly a tension symptom, and often in this astonishingly brief period he will report complete relief. We have used this test in a large number of cases presenting this confusing problem in diagnosis, with frequently gratifying results. This paper constitutes a report on our first series of such cases.

#### METHOD AND MATERIAL

*Method*—The patient's symptoms should be sufficiently acute at the time of injection of the amytal to make possible to the awareness of the patient an appreciable degree of relief. The patient is therefore instructed, if he is hospitalized, to put in a call for the house physician when his complaint is most acute. If he is an ambulatory patient or an outpatient, he is instructed to await the period when his symptoms are most distressing and then come to the physician's office at once. We have also made use of the emergency room of the hospital for this purpose, keeping sodium amytal available there and undertaking to have a house physician respond to such calls as promptly as possible. If the patient is hospitalized, no special preparations are required, but on the completion of the test the floor nurse is advised that the patient has received a certain amount of the drug, and orders for observation are given. In most instances the patient's sensorium will in no way be impaired, but a few patients may manifest drowsiness, confusion, incoordination or, rarely, excitement. Ambulatory patients should be accompanied by a responsible adult, and adequate means of transportation home should be available in the occasional cases in which these side effects occur.

The patient is allowed to recline, and data on the exact nature and magnitude of his symptoms are elicited and recorded. Before the amytal is injected, the patient is encouraged to describe his difficulties as accurately as possible, and he is examined physically as completely as is necessary. He is told that he will be given an injection that may relieve his symptoms somewhat, but unduly strong suggestion is not attempted. The patient is warned, also, that he may note some dizziness immediately after the drug is injected but that this is harmless and will pass off.

The solution of sodium amytal should be freshly prepared, being dissolved in distilled water or in isotonic solution of sodium chloride just before injection.

*Data in Cases of Anxiety Symptoms Treated with Intravenous Injections of Sodium Amytal*

Presenting Symptom (by Systems)	Possible Diagnosis	Symptoms	
		Symptoms Entirely Relieved by Sodium Amytal	Not Relieved or Only Partially Relieved by Sodium Amytal
Musculoskeletal			
Headache	Tension headache	22	5 (75 90% relief)
	Migraine (?)	1	0 (25% relief)
	Post lumbar puncture headache	4	3
Pain in shoulders and neck	Cervical neuralgia	3	0
Facial pain	Trigeminal neuralgia	3	0
	Sinusitis	1	0
Dizziness	Meniere's syndrome (?)	3	0
Ringing in ears	Meniere's syndrome (?)	1	0
Incoordination, unsteadiness of gait, (tremor), (blurring of vision)	Multiple sclerosis (?)	2	0
Pain radiating down leg	Sciatica	1	0
	Postoperative lame back	0	1 (made worse)
Gastrointestinal			
Nausea and/or vomiting	Ulcer or tumor (?)	23	1
Difficulty in swallowing	Esophageal ulcer (?)	2	0
Anorexia	Psychogenic	12	0
Epigastric distress (diarrhea)	Ulcer (?)	4	1 (50% relief)
Cardiovascular			
Anginal pain, (hot flashes), (palpitation), (tachycardia)	Angina pectoris (?)	2	0
Genitourinary			
Dysmenorrhea (frequency of urination)	?	5	2

The solution should be clear and colorless, occasionally we have encountered a brown or yellow solution, which may be attributed to impurities, such a mixture is discarded. We have been accustomed to use a solution containing 1 gram (0.065 Gm) of sodium amytal in each cubic centimeter of solution, but other proportions are, of course, feasible. In most instances we have available, in the syringe, 4½ grains (0.29 Gm) of the drug. One-half cubic centimeter (½ grain [0.032 Gm]) of the solution is injected rapidly, and during the next thirty or forty seconds the patient is asked whether any improvement has been noted. There is usually no noticeable effect from this small amount, but occasionally the patient will report a definite degree of relief. Another 0.5 cc is then injected, followed by questioning as to the extent of relief, and about one minute after the injection is started, the third 0.5 cc is given.



Usually 15 cc ( $1\frac{1}{2}$  grains [0.097 Gm]) is sufficient to produce significant relief, yet such an amount is so small that no drowsiness is evident, and no true analgesia can be said to have been produced. If the mitigation of the complaint is pronounced, no additional amytal is given. If the amelioration is only partial, however, it may be desirable to administer further portions of the drug, evaluating the persistence of symptoms as the injection continues and having in mind that as the total dose mounts many obscuring factors enter the picture.

Whether in the hospital or at home, the patient is observed carefully after the test to determine the interval of freedom from his symptoms.

*Material*—More than 80 cases in which this test has been employed have been documented. The presenting symptoms are itemized in the accompanying table, where they have been classified according to the pattern of anxiety in which each is likely to find place. The arrangement of patterns of anxiety used here is a modification of that outlined by Cameron<sup>1</sup> and will be seen to embrace three categories of symptoms. The first column lists the presenting symptoms which patients exhibited to the physician, and the second column enumerates the organic illnesses considered as likely to account for the various symptom. It should be stressed that we have not encountered every possible symptom of tension in this series of difficult diagnostic problems. The entries enclosed in parentheses in column 1 of the table represent anxiety symptoms which have not as yet come to our attention in accredited cases and are considered of controversial origin. A glance through the list, however, makes it evident that any one of these symptoms may appear at times of debatable origin.

## PAIN

### HEADACHE

The largest group of cases falls in the category of symptoms referable to the musculoskeletal system, and the bulk of this group are cases in which pain was manifested in some form. The most numerous single class is that which includes different types of headache. The headaches were of many varieties, ranging from "full feelings" in any part of the head to headache described as severe, disabling and intensely painful. The headaches have been characterized as "spasms" and as "throbbing," "twinging," "piercing," "gnawing" and "torturing." Patients have described them as "bursting," as "feeling as if my brain were too big for my skull" or as "seeming as if some terrible pressure were trying to get out." The differential clinical diagnoses considered at one time or another included, among others, brain tumor, cervical neuralgia, migraine, hypertensive encephalopathy and syphilis of the central nervous system. Some headaches were of recent origin, while others had persisted for months or years, with little significant abatement.

The patient in whom the test is clearly successful will have no residuum of distress but will express, often spontaneously, great relief and complete freedom from pain and a feeling of well-being. This rapid lifting of discomfort is especially impressive to both patient and physician.

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<sup>1</sup> Cameron, D. E. *Am J Psychiat* **101** 36-41 (July) 1944

in cases of long-standing headache, which have remained unrelieved for months, or even years

The awareness of reduction of tension has been expressed by the majority of patients, who usually describe the change as one of "relaxation" The symptoms of tension should be elicited by questioning before the injection of sodium amytal, as part of the case history of each patient In most instances a definite constellation of anxiety or tension symptoms may be plotted, the most frequent pattern being that of musculoskeletal tension The relief from these accompanying symptoms usually parallels the abatement of the headache, and the patient may state "The drawing feelings in my neck and eyes are gone", the tightness in my stomach has disappeared," or "the tightness in my arms and shoulders has gone"

Occasionally patients report a feeling of drowsiness concomitant with the sense of relaxation The drowsiness is not marked, and no patient has fallen asleep with the injection of  $1\frac{1}{2}$  grains or less of sodium amytal In a few instances patients who had been given between 2 and 3 grains (0.132 or 0.195 Gm) disclosed, on subsequent visits, that they had napped on returning home The question of the analgesic power of intravenous administration of sodium amytal is posed by this aspect of our results It must be pointed out that the dose of  $1\frac{1}{2}$  grains of sodium amytal is sufficient to relieve the headache in most instances and results in no subsequent drowsiness It is unlikely that so marginal a sedative dose will have analgesic potency, especially when symptoms are severe Furthermore, relief from pain usually lasts longer than any possible pharmacologic effect of the drug This will be considered in a subsequent section of the paper

In each of the 22 cases of headache designated in the table we were able to effect prompt and unmistakable relief by means of the intravenous injection of less than 3 grains of sodium amytal The usual dose was  $1\frac{1}{2}$  grains, but the dose required for complete relief in some instances was as low as  $\frac{1}{2}$  grain (0.032 Gm) In a few cases 3 grains were necessary, yielding at times only partial amelioration The case was not considered as meeting our requirements for inclusion in this series unless this partial relief was estimated as at least 75 per cent In the series of cases in which significant relief from headache was obtained several may be presented as typical

*Tensional Headache*—The following cases are cited

A man aged 26, a defense worker, for six months had had intense headaches, which started in the occiput and radiated over the vertex and down the back of the neck He had received a series of injections of vitamin preparations and had secured no relief from acetylsalicylate acid and codeine The pain was fairly constant but was more intense at the end of a day's work With the injection of 1 grain of sodium amytal, the patient noted that the headache was gone but that there was some

stiffness of his neck. This was relieved with injection of  $\frac{1}{2}$  grain morphine, to give the patient complete relief of his symptoms. Psychiatric interviews revealed a number of problems which were judged to be contributory factors. He was given mild daily sedation and psychotherapy. When last seen the patient still had occasional headaches, but they were never so severe or so prolonged as formerly.

The duration of alleviation of headache is inconstant. In several instances the pain remained absent for weeks, whereas in others it recurred within a few hours.

The longest period of freedom was seen in the case of a woman aged 22, whose headache had persisted for more than a year. During that time she professed to have had no period of complete freedom from pain. After the injection of 2 grains of sodium amytal she acknowledged that the headache had vanished and stated that she was more relaxed and more content than she had been in over a year. She reported by telephone the next day that she was still free from pain, and she remained so for more than six weeks. During this time she felt so well that she was able to proceed with her plan to enter nurses' training, an undertaking she had postponed indefinitely because of the headache. The importance of associated psychotherapy in this case, as in all the others here discussed, is of course beyond dispute. The sodium amytal test is to be considered merely an adjuvant to diagnosis and therapy.

This patient's headache began to return in a mild form about six weeks after the first injection, despite several psychotherapeutic interviews. A second injection of amytal was given, complete relief again being obtained with 2 grains of the drug. The patient has now been free from symptoms for about three months and has also shown a decided improvement in the larger picture of her psychoneurosis.

In contrast to this case are those in which relief is gained for but a brief period, sometimes only a few hours. Although the duration is so limited, it is nevertheless evident that in many cases the appeasement persists longer than the known pharmacologic effects of the sodium amytal would lead one to expect.

One patient, for example, obtained almost complete relief by means of 1 grain of sodium amytal and was free for the remainder of the day and for the major portion of the next day, beginning to perceive the return of the headache in the evening. Subsequent injections were necessary, but during this period the underlying factors in her psychoneurosis were probed and intensive psychotherapy was instituted.

In several instances it was clear that the distress recurred as the sedative influence of the drug wore off. It should be stressed, however, that the most signal value of the test is the rapid, sometimes abrupt, deliverance from pain by a small dose of the drug. This strongly suggests the "tensional," or "nonorganic," origin of the symptom in many cases. The fact that relief does not persist indicates the broader problem of the whole psychoneurosis.

A patient securing only transient relief was a woman aged 28, who described her headache as "a terrible aching and pulling on the back of my head." She was able to carry on her work as a secretary, but without enjoyment, and had

surrendered her usual recreational and social activities. She visited the emergency room of the hospital several times, usually in the early evening, and with injection of from 1 to 2 grains of sodium amytal found solace, which she described as an "oasis" in the continual distress she felt. Her well-being usually persisted for the remainder of the evening, and she was able to fall asleep more readily than was customary. The following morning, however, saw the headache restored to its original severity. The patient refused to return regularly for psychotherapy and has as yet refused to enter the hospital for more intensive study, but the results of the amytal test, together with the history and the absence of positive physical signs, make the diagnosis of tensional headache probable.

A definite proportion of patients did not secure significant relief. One reason for failure of sodium amytal to give them relief was the probable presence of some organic cause. In certain patients, however, no organic factor was unearthed, yet the mitigation of the headache by means of sodium amytal was not sufficiently well defined to warrant their being included in the group with tensional headaches. Instead of replying within one to five minutes after the injection of the amytal that the headache had vanished, the patients sometimes qualified their statements by expressing uncertainty.

One patient explained that her headache had lessened somewhat but said, "There's still a funny feeling of pressure in the back of my head, sort of uncomfortable, and a little ache in the front."

A second patient who was included among those who failed to obtain relief described her headache, after sodium amytal had been injected, as "still present, I think, but it seems to be screened out a little by dizziness." The feeling of dizziness was sensed by many patients, but most of them found, nevertheless, that it did not obscure their awareness of definite relief of the headache. Thus, one patient stated, "My headache is gone completely, for the first time in months. I feel a bit dizzy, but no more than one cocktail might make me feel, the sense of relaxation is glorious."

*Migraine*—The numerous problems of migraine and its psychosomatic implications are at issue here, but the evidence which has emerged in the present series is inadequate for us to assess the question basically.

Four patients with previous clinical diagnoses of migraine were tested, with inconclusive results. Three patients had partial alleviation of their headache, each patient estimating his relief as 25 per cent. One of these was a man aged 40 with a history of migraine for several years. Several therapeutic regimens had been followed, without complete relief from any. The injection of from 1 to 2 grains of amytal yielded partial relief, which lasted from one to seven or eight days, four such injections were given. The patient was given sodium amytal to take by mouth, in a dosage of 1 grain three times daily, with instructions to take 2 capsules of 1 grain each when a sudden, severe headache manifested itself. He has now been receiving this medication for a sufficient period to permit comparison of its value with that of ergotamine tartrate, the only drug previously used which had offered significant aid, and he reports that the amytal is definitely more salutary. The psychoneurotic background of this patient has been investigated at some length, and regular psychotherapy has reenforced the use of the drug.

Optimal relief is obtained by using ergotamine tartrate in combination with sodium amytal

The pressure of "tensional" headache superimposed on the headache of migraine is recognized by many observers, notably Wolff<sup>2</sup> Ergotamine tartrate followed by injections of sodium amytal might well afford more complete relief to sufferers of migraine than ergotamine alone

The most startling relief was experienced by a hospital technician, aged 37, who had had periodic headache for the previous eighteen years The diagnosis of migraine had been made, but she secured such inadequate relief from prescribed medication that she was forced to take to bed for one or two days during each episode She was given 1 gram of sodium amytal by intravenous injection at the beginning of a typical attack of headache, with almost complete and immediate relief A second headache, four weeks later, was relieved at home by taking secondal sodium ( $1\frac{1}{2}$  grains [0.097 Gm]) orally For the past three months the patient has had no recurrence of symptoms

*Post-Lumbar-Puncture Headache*—Seven patients with post-lumbar-puncture headache were tested with sodium amytal by the method noted All injections were administered at least eight hours after the lumbar puncture, and usually on the following day Four patients noted significant and rapid relief

One of these was a kitchen helper aged 38 who had first had seizures about two years prior to admission to the hospital After lumbar puncture he had severe headache and nausea, which were relieved by lying down These symptoms persisted for two days despite medication with acetylsalicylic acid and codeine On the third day he was given sodium amytal,  $1\frac{1}{2}$  grains, with complete relief of pain This relief persisted all that day, and the patient was discharged the following day, still free of headache In another patient, however, freedom from pain lasted one hour, and the headache returned with its former severity

*Head Pain Other Than Headache*—The face, neck and shoulders are common sites for the appearance of the "drawing pains" which form a part of the musculoskeletal pattern of anxiety These regions, too, are areas where differential diagnosis as to the origin of the pain may constitute a formidable problem Included in the present series are several cases of this type, in each of which the usual clinical and laboratory tests were uninformative but the headache was demonstrated to be of tensional origin by the amytal test

Pain in the posterior part of the neck and shoulders, resembling cervical neuralgia, was relieved in 3 cases—all those which were investigated by this means In each instance there was pain sufficiently severe to bring the patient to his physician, and in 2 cases the pain was sufficiently agonizing and persistent to make hospitalization advisable when the local physician was unable to ascertain the cause Careful histories revealed the general psychoneurotic background of the patient's behavior,

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2 Wolff, H G J Omaha Mid-West Clin Soc 5 33-39, 1944

but the pain in the shoulder could not be considered incontrovertibly an anxiety symptom until the amytal test was applied

Facial pain resembling trigeminal neuralgia was encountered in 4 cases in this series, and pain simulating that frequently present in sinusitis was seen in 1 case. The diagnostic problems were similar to those noted previously, in that trigeminal neuralgia was judged to exist after other possibilities had been exhausted by roentgenographic and other examinations. The distribution of pain in each case was not closely characteristic of trigeminal neuralgia, nor was the type of attack representative, but no other diagnosis seemed feasible to the referring physicians. Sodium amytal evoked significant relief in each case.

The most perplexing case was that of a nurse aged 42, whose trouble had been diagnosed as *tic douloureux* by her referring physician. She had been thoroughly studied for evidence of sinusitis, a complaint she had voiced intermittently for several years, without anything positive coming to light. She described her distress as being fairly constant on a low grade level, with frequent episodes of harsher pain, sometimes so unrelenting as to cause crying. The pain involved the left side of her face, beginning near the ear and spreading to the nose, temple and chin, and being accompanied with headache. Later in her stay in the hospital she complained that there was some involvement of the opposite side of the face, though to a less, and much more bearable, degree. This case was at first studied as purely neurologic, and the lassitude and dejection she displayed were considered to stem from her oppressive pain. It quickly became apparent, however, that emotional factors were of paramount import, and interviews disclosed a multitude of conflicts and anxieties. It was still not possible to establish the tensional origin of the pain, although our suspicions were aimed in this direction. The injection of 2 to 3 grains of sodium amytal brought about startling relief, which persisted for several hours. The patient's subsequent course included intensive psychotherapy, bolstered by several injections of amytal at critical moments of distress. It became evident that her tensional symptoms were colored by an undercurrent of depression, which did not respond to psychotherapy. The element of depression was soon judged so grave, although somewhat hidden, that electric shock therapy was decided on. She improved rapidly during a course of six shocks, and on discharge was almost completely well—not depressed, and free from her facial pain, although still voicing many of her basic anxieties.

#### PAIN IN PARTS OF THE BODY OTHER THAN THE HEAD

"*Sciatica*"—Another case of pain difficult to diagnose was one of sciatica.

A woman aged 30 had been under treatment for sciatica. The attacks usually began mildly with shooting pains down the posterior aspect of the left leg. She was placed on a regimen of rest and physical therapy but did not improve rapidly, so her physician brought her into the hospital, where roentgenologic and neurologic examination and studies of the spinal fluid showed nothing abnormal. One evening she complained that the pain was increasing, and as the night went on she insisted that the anguish was becoming unbearable. Codeine and seconal sodium brought some relief, but a second dose of seconal was necessary to produce sleep. She complained of still greater agony the next day, in addition, she was agitated,

apprehensive and tremulous. Sodium amytal was injected slowly. When only  $\frac{1}{2}$  grain had been introduced, she began to relax, said she was less tense and reported definite improvement in the pain in her leg. With only 1 grain of amytal injected into her blood stream, she began to express wonderment that her wretchedness had left her so completely and reported that her leg was free from pain. She demonstrated this fact by moving the limb readily, although she had for the previous several days held it almost immobile. She was discharged from the hospital shortly afterward, later she had two episodes of pain, which were again relieved with sodium amytal. With psychotherapy she remained symptomless for almost a year.

*Postoperative Lame Back*—In only 1 instance was pain made worse with sodium amytal.

A man aged 33 had been operated on for a ruptured intervertebral disk about eight months prior to the present admission. At that time a fusion of the spinal vertebrae had been done. After recovery the patient was subject to recurrent pain in the back, which radiated down both legs and was relieved by his remaining in bed for a time. However, on his resuming work the pain would recur with its old intensity. He was seen by several physicians, one of whom told him that he had a "chronic lame back" and another stated, "It's just your imagination." To alleviate his pain, the patient began to drink more heavily than before and was first seen by us in the psychiatric ward during an acute alcoholic episode. When he recovered from the effects of the alcoholism, he was discharged and made a good social adjustment, with the help of Alcoholics Anonymous, Inc, which helped him secure a job as a dental mechanic. After working for several weeks at tasks requiring his sitting for eight hours a day, the patient began to complain of severe pain in the back. He was given an injection of 2 grains of sodium amytal, but this only increased the pain. He was thereupon taken into the hospital, where an intraspinal injection of iodized poppyseed oil revealed still another ruptured intervertebral disk. This was removed, and the patient has had no recurrence of the symptom since the operation, three months ago.

*Dysmenorrhea*—One of the most perplexing and annoying symptoms is that of dysmenorrhea. Often women are relieved by surgical procedures, such as dilation and curettage, placement of stem pessaries and suspension of the uterus. Hysterectomy is at times resorted to in cases of persistent and incapacitating dysmenorrhea. We have treated 7 patients with dysmenorrhea and have failed to afford relief in only 2 of these patients. Each patient was given  $1\frac{1}{2}$  grams of sodium amytal intravenously. Relief from pain persisted throughout the day (usually the first day of menstruation) except for minor, negligible cramps.

*"Anginal" Type of Pain*—We have diagnosed as tensional the pain of 2 patients with syndromes of angina pectoris by relieving symptoms through intravenous injections of sodium amytal.

One of these patients, a woman aged 52, whose first husband had died of coronary occlusion, experienced repeated pain in the precordium, which radiated down the left arm. Electrocardiograms on several occasions were normal.

Glyceryl trinitrate served to increase the symptoms, which responded completely to intravenous injections of sodium amytal in small doses

### SYMPTOMS OTHER THAN PAIN

*Gastrointestinal System*—Many tensional symptoms are associated with the gastrointestinal tract. Included among these are nausea and vomiting, difficulty in swallowing, anorexia and epigastric distress. In 43 cases the symptoms were diagnosed as being cardinally functional by means of sodium amytal, which, injected intravenously in small doses, granted almost complete relief in all but 1 case.

Anorexia, even in depressed patients, is continually relieved by the administration of a relaxing dose of sodium amytal (usually  $1\frac{1}{2}$  grains) just before each meal. In the 12 instances of anorexia cited in the table, the patient was enabled by this method to eat entire meals without difficulty. Furthermore, none of these patients complained of a sense of fullness or nausea afterward.

One patient, a woman aged 53, had been undergoing medical treatment for difficulty in swallowing. Fluoroscopic examination showed a dilated esophagus, and the diagnosis of cardiospasm was made. Esophagoscopy failed to reveal any organic lesion which might be responsible for her condition. Sodium amytal, given intravenously in doses of 1 to  $1\frac{1}{2}$  grains during meals, when the patient complained of obstruction and regurgitation, enabled her to swallow without difficulty. The same sedation before meals gave her complete relief and did away entirely with the feeling that food was lodging in the esophagus. Her weight, which had dropped from 130 to 100 pounds (59 to 45.4 Kg), began to rise. She was discharged with instructions to take several grains of sodium amytal before each meal. This procedure, together with psychotherapy, has allowed her to continue for the past two months without recurrence of her difficulty.

Twenty-three patients with nausea and/or vomiting obtained complete relief from their distressing symptoms, although for some of them a tentative diagnosis of peptic ulcer had been made.

Another patient with many symptoms of tension had been treated medically for diarrhea over a period of four years. She was seen by us because of "nervousness," incoordination and feelings of tension. These symptoms had been precipitated by the nature of her work, which required that she complete an assignment by a certain date. Although the patient realized that she should slow her pace, financial considerations made this impossible. After pointing out the hazards of continuing her work, we offered to support her by injections of sodium amytal at times when she was particularly distressed, with the understanding that when her work was finished she would enter the hospital for study and psychotherapy. Injections were given about every two days, with some relief of symptoms; interestingly, the patient reported that for the first time in years she had a formed stool, that she no longer suffered from diarrhea and that she had gained 7 pounds (3.2 Kg) in three weeks.

The 1 patient with gastrointestinal complaints who failed to secure relief was a woman with severe nausea and vomiting which failed to yield to the relaxation produced by the drug and who finally required gastroenterostomy to obtain release from the symptoms. Adhesions were found around the duodenum, but no reason for a mechanical block of the pyloric outlet was discovered. The patient was discharged after an uneventful postoperative course and returned to her home.



Reports from one of her physicians indicated that the nausea and vomiting recurred, but further contact with this patient could not be made and we are uncertain as to her outcome

*Musculoskeletal System*—Many of the symptoms listed in the table under the musculoskeletal system have been discussed in connection with pain. The symptoms not discussed include those occurring in several cases tentatively diagnosed as Meniere's syndrome because of dizzy spells and ringing in the ears and a disturbance in 2 cases diagnosed as multiple sclerosis because of incoordination and equivocal signs. The patients were completely freed of their symptoms by injections of sodium amytal.

#### COMMENT

The broad concept of this paper is the contention that symptoms resulting from tension or anxiety will frequently disappear with mild sedation. In order that the effect of the sedative be fully appreciated, it should be given intravenously, to reduce the time between its administration and its effect. Furthermore, to eliminate whatever analgesic effects may be attributed to the drug, just enough sedative should be given to produce relaxation. This has been accomplished with sodium amytal in average doses of  $1\frac{1}{2}$  grains. The injections are made when the symptoms are at their height. Even when pain is the symptom, the mechanism of relief may be attributed to the tension-relaxing phenomenon, since the analgesic property of such small doses of sodium amytal is slight. None of our patients were put to sleep with these injections. Moreover, the relief afforded by the drug in most cases far outlasted its pharmacologic effect.

It should be stressed that this test should not supplant any of the customary psychiatric diagnostic procedures but is best utilized as an adjuvant to these procedures. It cannot replace the careful, comprehensive study of each psychoneurotic patient, involving the psychiatric interview, projective procedures for unearthing conflicts and other techniques. It has served, however, in more than 80 cases encountered in a period of nine months to curtail the period of hospitalization of many patients.

Many patients are recognized as displaying definite neurotic patterns but as having also somatic complaints which are not necessarily part of this pattern and are therefore difficult to evaluate. For example, severe headache may be a cardinal complaint in a patient with chronic anxiety but may not have an organic basis. A careful history may reveal the place of the headache in the psychoneurosis, or psychotherapy may eventually relieve the headache, together with the other symptoms. It is felt that by means of this test, however, the proper assessment of the headache can be made more quickly, thereby saving both time and the expense of repeated searching for an organic foundation.

Although the test should not replace standard diagnostic procedures for organic illness, it has proved valuable in its role of focusing attention on functional elements in cases in which physicians have kept patients hospitalized for weeks in unavailing repetition of tests for organic disease.

The amytal test should be considered primarily a diagnostic measure. The problem of diagnosis in psychiatry is somewhat different from that in other specialties, for therapy goes hand in hand with diagnosis. From the moment the psychiatric interview begins, whether involving face to face discussion, projective procedures or use of the needle and syringe treatment of the patient is instituted. The very willingness of the interviewer to probe into psychiatric problems should hold his awareness that he assumes therapeutic responsibility also. It is apparent therefore that no psychiatric test can be deemed solely a test. There must be continuous integration with therapy, in whatever degree required. The utilization of the amytal test must be governed by this tenet. Although primarily a diagnostic method, the relief of pain, the explanation of what is being attempted, the assumption of the patient-physician relationship—all of these constitute therapy and are inseparable from the simple diagnostic test. In the case histories previously cited, therefore, the diagnostic and therapeutic elements are necessarily mingled. Emphasis in this paper, however, is placed on the diagnostic value of the test.

The usefulness of this test is of course limited by the inherently complex nature of psychiatric problems. Its applicability, however, proved wider than we at first appreciated. Over the period of about six months during which our cases were collected, almost every service of a 600 bed general hospital called on the psychiatric department for consultation when this test proved fruitful. Considerable enthusiasm for the test was aroused in the departments of surgery, internal medicine, orthopedics and gynecology, where in puzzling cases the drug granted relief from symptoms after the usual procedures proved unavailing and the way was thus paved for future management. In many cases this initial relief of pain convinced patients and their families who were resistive to psychiatric consultation that further psychiatric therapy might be helpful. This is an important consideration in the care of private patients who refuse, because of their own or their families' unwillingness, to permit the sometimes slow tempo of psychotherapy to prove its value.

No one group of problems considered here is a statistically large sample, and the conclusions drawn for any one symptom complex must be considered tentative—indeed, they are not conclusions so much as reports on clinically interesting and therapy-resistant material. But although no one syndrome has been studied in large numbers, the fundamental pattern of the relief of pain, vomiting and other symptoms

by a tension-reducing measure has emerged in the entire series here reported

This test shows that certain symptoms are based on what, for want of a more specific term, we call a tensional foundation. It also strengthens the belief that in many cases of organic disease there is a superimposed element in the system which is due to tension alone—probably the portion which makes the symptom so intense.

There has been a recent tendency to combine analgesic drugs with a sedative for optimal results. This is an empiric way of treating a symptom whose basis is not truly known. By use of the amytal test it can be determined whether the symptom is, in general, organic or functional and the proper drug utilized. In some instances the combination of an analgesic and a sedative drug would be more effective. Another advantage afforded by this test is that it can be used to prove the existence of tension to the patient and thus to lay the foundation for the future psychotherapy.

It must be stressed again that this test is primarily a diagnostic measure, that it should be considered only a small portion of the psychotherapeutic regimen and that each patient must be studied carefully as a problem in human behavior.

### CONCLUSIONS

- 1 Anxiety or tension states may give rise to symptoms referable to many systems of the body, even in patients not considered psychoneurotic.

- 2 Symptoms due to organic disease may be exacerbated because of tension.

- 3 Sodium amytal in average doses of  $1\frac{1}{2}$  grains (0.097 Gm.) given intravenously will frequently relieve a symptom which is entirely due to tension within one to five minutes.

- 4 The same amount of sodium amytal will relieve that portion of the symptom due to tension in instances in which tensional pain is superimposed on pain of organic cause.

- 5 Sodium amytal in small doses can be used as a diagnostic test to separate symptoms of organic disease from tension symptoms.

- 6 The test should be used only to supplement thorough physical and psychiatric investigation.

# Abstracts from Current Literature

EDITED BY DR BERNARD J ALPERS

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## Physiology and Biochemistry

ELECTRO-ENCEPHALOGRAPHY IN CASES OF SUB-CORTICAL TUMOUR W G WALTER  
and V J DOVEY, J Neurol, Neurosurg & Psychiat 7 57 (July-Oct) 1944

By means of automatic analysis with an apparatus which traces a frequency histogram over the primary record, Walter and Dovey were able to make an exact analysis of the electroencephalograms in 31 cases of subcortical tumor. In all cases significant activity in the 4 to 7 cycles per second band was noted. Of these, good correlation between the superficial location of this rhythm and the deeper effects of the new growth was shown in 21 cases. These cases were divided into three categories, as follows: (1) Cases of superficial tumors spreading into subcortical structures. The site of the tumor exhibited activity of 1 to 3 cycles per second, or delta waves, while the adjacent areas and temporoparietal regions showed 6 cycles per second activity, or theta waves. (2) Cases of deep tumors spreading outward. The main feature was 6 cycles per second activity in the cortex above the tumor and in the temporoparietal regions. (3) Cases of deep tumors not affecting the cortex. The 6 cycles per second rhythm was the only significant abnormality, and this was usually related to the parietotemporal region. In cases in which the new growth was more widespread, the 6 per second rhythm was seen whenever basal structures were affected. Thus, an electrical activity of about 6 cycles per second is associated with involvement of subcortical structures, and this theta rhythm is located in the parietal and temporal regions.

MALAMUD, San Francisco

THE EFFECT OF PERCUSSION OF NERVE. D DENNY-BROWN and C BRENNER,  
J Neurol, Neurosurg & Psychiat 7 76 (July-Oct) 1944

Denny-Brown and Brenner investigated the effects of lesser degrees of injury to peripheral nerves in order to determine the nature of the structural change underlying the transient disturbance of function with such injuries. They found that a single percussion of a nerve trunk resulted primarily in damage to the myelin sheath and probable longitudinal rupture of the sheath of Schwann, with escape of damaged myelin into the endoneural spaces but without interruption of the axis-cylinder, even with severe blows. At the site of injury a localizing swelling, or pseudoneuroma, developed as a result of edema associated with the rapid appearance of large numbers of histiocytes. This reaction was related to the breakdown of myelin and occurred if regeneration was prevented by proximal ligature. It was prevented if the blood supply was interrupted. With such a moderately severe lesion, since axis-cylinders remained largely intact, there was retention of sensation with transient complete block of impulses in motor fibers. This dissociation in function closely resembled that caused by ischemia induced with compression. The degree of edema and demyelination was lessened by concomitant rupture of the perineurium and decompression of the edema, indicating that ischemia accompanied the edema but was not an essential feature of the mechanism of the lesion. The phagocytic reaction was derived from histiocytes, the Schwann cells playing no part in it. A partial lesion produced transient paralysis, lasting three to four days, without loss of gross sensation. Here a

pseudoneuroma was also present, the majority of the axis-cylinders being deprived of myelin in passing through the neuroma but recovering it below. If the axis-cylinder was transversely interrupted by the percussion, degeneration occurred in the distal portion of the nerve fiber, and regeneration was extremely rapid and complete. Regeneration of axis-cylinders in intact Schwann tubes took place by the initial production of a large number of fibrils by the parent axis-cylinder, early maturation of one of these and resorption of the remainder. Delay in regeneration resulted when the perineurium was ruptured, causing herniation of nerve fibers and endoneurium with formation of a true neuroma. Percussion of a nerve trunk in the process of wallerian degeneration led to liberation of intratubal phagocytes by the mechanism of traumatic splitting of the tube of Schwann cells.

MALAMUD, San Francisco

#### THE ELECTRO-ENCEPHALOGRAPHIC LOCALIZATION OF INTRACRANIAL NEOPLASMS

W A COBB, *J Neurol, Neurosurg & Psychiat* 7 96 (July-Oct) 1944

In an analysis of the electroencephalograms of 125 patients with intracranial space-occupying lesions, Cobb found that rapidly growing lesions near the free convexity of the cerebrum lend themselves most readily to localization. Thus, about one-half the cerebral tumors were correctly localized, as compared with only 3 of 21 subtentorial tumors and none of the midline or basal tumors. Localization was difficult in the case of parasagittal tumors, especially meningiomas. There was a greater tendency to slowing of the alpha rhythm in cases of tumor than is observed in cases of traumatic injury or of epilepsy. At times a noticeable asymmetry of the alpha rhythm was a useful aid in lateralization. The effect of increased intracranial pressure on the electroencephalogram was not characteristic, the abnormal waves being generalized and usually possessing a frequency of about 2 to 4 per second, irregular rhythm and lower amplitude than that of the alpha rhythm. This electroencephalographic pattern could not be distinguished from that of cortical atrophy, vascular disease or other diffuse condition. There was no direct relation between these changes and the height of intracranial pressure or the degree of papilledema, but there was some correlation with the state of consciousness. The local effects were not always distinguishable from the generalized effects of high pressure, but as a rule high amplitudes and very slow frequencies were uncommon with the latter. The usual record in a case of tumor was a mixture of slow frequencies.

The "ideal" means of localization is the finding of phase reversal of the slow waves, but not infrequently one must depend rather on their maximum intensity. A 4 to 7 per second frequency band, or theta rhythm, was found to be associated with lesions in the region of the third ventricle. In the opinion of the author minimal general change may prove to be just as diagnostic in cases of tumor as the presence of a gross dysrhythmia.

MALAMUD, San Francisco

#### THE ELECTROENCEPHALOGRAM IN TRAUMATIC EPILEPSY

D WILLIAMS, *J Neurol, Neurosurg & Psychiat* 7 103 (July-Oct) 1944

Williams investigated the relationship of abnormalities in the electroencephalogram of patients with head injuries to subsequent onset of traumatic epilepsy by comparing the tracings of the following groups: (1) 241 normal healthy controls, (2) 234 patients with head injury but without epilepsy, (3) 210 patients with traumatic epilepsy, (4) 275 patients with idiopathic epilepsy and (5) 42 patients who were examined with the electroencephalograph before and after the onset of traumatic epilepsy.

The results showed that larval epileptic outbursts were invariably associated with overt fits, being present in 9 per cent of patients with traumatic epilepsy, in 27 per cent of patients with idiopathic epilepsy and in none of the subjects who

had not experienced epileptic fits, including those with head injury. Other paroxysmal outbursts, on the other hand, were nearly as common in patients with head injury who did not have fits as in those who did. Thus, the presence of other paroxysmal outbursts in cases of post-traumatic states does not necessarily indicate the development of traumatic epilepsy. Nonspecific abnormalities were not affected by the presence of epilepsy and represented results of injury or pre-traumatic abnormality. The incidence of paroxysmal epileptic outbursts was higher in the group of patients with penetrating wounds than in those with closed injuries of the head, while nonspecific abnormalities were equally common in the two groups. A comparison of the records made before and after the onset of fits showed that the characteristic episodic changes often appeared in the electroencephalogram before the onset of traumatic epilepsy. Foci of abnormal discharge were found in a larger proportion of patients with traumatic epilepsy than in patients with idiopathic epilepsy. In the opinion of the author, a distinction is to be made between the immediate, or primary, effects of trauma on the electroencephalogram which are reversible and transient, and the remote, or secondary, effects, which are irreversible and persistent and are usually associated with epilepsy. While the electrical disturbances associated with traumatic epilepsy and those occurring with idiopathic epilepsy differ in their frequency and site of origin, they are fundamentally similar. This conclusion may be compared with similar ones reached on histologic grounds.

MALAMUD, San Francisco

THE SCOPE AND LIMITATIONS OF VISUAL AND AUTOMATIC ANALYSIS OF THE  
ELECTROENCEPHALOGRAM G. D. DAWSON and W. G. WALTER, *J. Neurol.,  
Neurosurg. & Psychiat.* 7:119 (July-Oct.) 1944

Visual inspection and measurement are often inadequate to analyze the more complex types of change present in an electroencephalographic record. Dawson and Walter use an electromechanical method of automatic analysis, by means of which mixed rhythms are synthesized and the effects on the form of such rhythms of variations in the size and frequency of their components are demonstrated. Visual examination does not separate from masking rhythms those component rhythms in a record which are masked. Moreover, only rhythms which are larger than others can be measured by the visual method, but those rhythms which are either comparable in size with or smaller than others are not measured by this method. To determine these, automatic analysis must be used. When the latter is not available, the use of closely spaced bipolar electrodes is of value, since it may demonstrate the presence of masked rhythms, although it does not measure their size. On the other hand, the limitation of automatic analysis is the inability of the method to record transient outbursts of brief duration and to express the phase relations of the components of a compound rhythm. The importance of the latter is seen in the simple cases of waves formed from a fundamental and one or two harmonics, as well as in the complex wave and spike discharges. Further investigations of these problems by full automatic analysis are indicated.

MALAMUD, San Francisco

### Neuropathology

HEPATO-LENTICULAR DEGENERATION (WILSON'S DISEASE) REPORT OF ONE CASE  
WITH SEVERE PORTAL CIRRHOSIS AND SPLENOMEGALY HARRY FREEDBERG,  
*Ann. Int. Med.* 22:418 (March) 1945

Freedberg reports the case of a 26 year old Italian woman with hepatolenticular degeneration who was closely observed over a period of six years. When she was first seen, she complained of extreme nervousness, periods of amenorrhea and coarse tremors of both hands. She adjusted fairly well, with little progression of symptoms, until five years after she was first studied, when she complained

of loss of weight of about 25 pounds (12 Kg), bleeding from the gums, increase in nervousness and the development of an abdominal mass

Physical examination revealed a protuberant abdomen with physical signs of ascites and evidence of splenomegaly. The liver could not be palpated.

The significant observations on neurologic examination were as follows: a constant grin, which remained relatively fixed, slow and monotonous speech, and some difficulty in swallowing. There were gross tremors of the head, protruded tongue and trunk and tremors of the extended hands, these tremors were increased with involuntary movement, especially on the left side. Slight tremor of the legs was apparent. There was a Warner hand on the left side. The deep reflexes of the upper extremities were of the basal ganglia type, that is, with each reflex response there was imperfect relaxation. This was also true to a less extent in the lower extremities. Examination with the slit lamp showed no evidence of a Kayser-Fleischer ring.

Rontgenographic examination showed extensive abnormalities involving the whole length of the esophagus. These consisted of tortuous defects of the mucous membrane. The changes were characteristic of extensive varicosities of the esophagus. The urine was normal. Studies of the blood revealed nothing of particular significance, except for anemia and negative Hinton and Wassermann reactions of the blood on two occasions and a positive Kahn reaction on two occasions.

Tests of hepatic function gave the following results. The prothrombin time was thirty-five seconds. The total cholesterol measured 107 mg, the free cholesterol, 40 mg, and cholesterol esters 67 mg, per hundred cubic centimeters. The bromsulfalein excretion test showed a retention of 50 per cent of the dye at the end of an hour. The icteric index was 12. The total bilirubin of the blood measured 14 mg, and the blood phosphatase 60 Bodansky units, per hundred cubic centimeters. The blood serum proteins measured 7.10 Gm, with 2.95 Gm albumin and 4.15 Gm globulin, per hundred cubic centimeters. The Takata-Ara test was positive in four tubes.

For several months prior to death the patient had hemorrhages from the mouth, associated with vomiting and tarry stools.

Changes of significance observed at necropsy, other than the presence of esophageal varices, splenomegaly and ascites were confined to the liver and brain. The liver was small, firm and uniformly nodular. Microscopic examination revealed definite thinning around many of the central veins, and a lobular pattern was present. In some sections there were broad areas of scarring and in others the lobules showed only slight vacuolation of some of the liver cells. A few portal areas showed slight increase of stromal connective tissue. The dura was not remarkable. The brain was described as being distinctly "porky" and edematous. On the left, in the region of the caudate nucleus, there were a grayish white area of apparent gliosis and some distortion of the relations of the nuclei to each other. The right side appeared to be entirely normal. The brain weighed 960 Gm.

Microscopic study of sections of the brain revealed no abnormalities except in the lenticular region, where there were occasional areas of loss of normal outline, with fraying of some of the structures and occasional foci of gliosis. Only an extremely rare large Alzheimer cell was seen. The appearance of the cortical cells showed no apparent lesion involving the third nuclear layer.

Freedberg reports this case because the changes affecting the liver far outstrip those observed in the lenticular nuclei, and death was directly related to cirrhosis of the liver. Wilson stated that the latter condition rarely, if ever, gives rise to symptoms during the life of the patient, and in the case described in the literature death was attributed to the cerebral involvement.

Tests of hepatic function which were performed before the patient's death indicated severe hepatic dysfunction. The positive Kahn reaction is explained by the hyperglobulinemia.

Freedberg believes that Wilson's theory, "that the liver is first affected and that the lenticular lesions follow as a result of some unspecified toxin which either originates from, or is not neutralized by, the damaged liver," is the most plausible explanation for the course of this patient's illness

GUTTMAN, Philadelphia

**PATHOLOGY OF THE LIVER IN EXTRAPYRAMIDAL DISEASE** G HEILBRUNN  
O FELSENFELD and P SZANTO, *J Nerv & Ment Dis* **102** 19 (July) 1945

The authors made postmortem examinations of the liver in 3 cases of post-encephalitic parkinsonism, 1 case of paralysis agitans and 1 case of Huntington's chorea and found mild and nonspecific structural changes, consisting of moderate periportal round cell infiltration, mild passive congestion and moderate fat infiltration at the periphery of the acini. The colloidal gold test of the blood serum, determination of the prothrombin time, the Weltmann coagulation test and the Lange-Heuer flocculation test were performed on 58 patients suffering from various extrapyramidal disorders, positive reactions being obtained in 85 per cent of the cases. The highest percentage of positive reactions (93 per cent) was found in 15 cases of Huntington's chorea. The authors believe that these results justify the conclusion that the liver manifests dysfunction in a high percentage of cases of extrapyramidal disease, but they feel that no conclusion as to its primary, secondary or correlated character is warranted.

CHODOFF, Langley Field, Va

**ANATOMICAL DEFECTS AND PATHOLOGICAL CHANGES IN CONGENITAL CEREBRAL ANEURYSMS** FRANCIS M FORSTER and BERNARD J ALPERS, *J Neuropath & Exper Neurol* **4** 146 (April) 1945

Forster and Alpers report their histopathologic observations on 8 patients with cerebral aneurysms. The arteries of origin were embedded in paraffin, sectioned serially and prepared with hematoxylin and eosin, Van Gieson's stain for elastic tissue and Masson's trichrome stain. The condition of the parent vessel in the entire series of sections, the constituent coats of the aneurysmal sac and the changes in the wall of the vessel at the origin of the aneurysm were studied.

The cases studied revealed a variety of changes in the elastic membrane, ranging from a complete membrane, through splitting and fragmentation to the complete absence of the membrane, with a sharp defect at the site of origin of the aneurysm. These observations indicate that there is a tendency for the elastic membrane within the aneurysmal wall to disintegrate and that this occurs without other evidence of degenerative change, either in the elastic membrane of the parent vessel or in other structures of the aneurysmal wall. The tendency toward destruction of the elastic membrane may proceed not only until the entire elastica of the aneurysmal sac is destroyed but until even the edge of the defect is sharpened.

The present series of observations conforms with the prevailing opinion that the defect in the media is congenital and indicates that the changes in the elastic membrane vary widely and are independent of degenerative changes elsewhere. This would seem to corroborate the explanation for degeneration of the elastica as given by Bremer. Because of these wide variations in the status of the elastic membranes of aneurysms that have arisen at bifurcations and from areas of defect in the media of the parent vessel, Forster and Alpers feel that such aneurysms should be considered congenital, regardless of the state of the elastic membrane. The changes in the elastica are secondary to the formation of the aneurysm, and minute classification on the basis of a variable anatomic feature does not seem warranted, particularly when the variability depends on the presence of the aneurysm in the first place.

GUTTMAN, Philadelphia



LEUCOENCEPHALITIS ASSOCIATED WITH PURULENT LEPTOMENINGITIS (MENINGO-LEUCOENCEPHALITIS) I MARK SCHEINKER, J Neuropath & Exper Neurol 4 164 (April) 1945

Scheinker reports observations in 7 cases of purulent leptomeningitis, in all of which there were widespread, diffuse, inflammatory phenomena involving the leptomeninges and large areas of the central and the subcortical white matter. The lesions in the white matter were inflammatory, hemorrhagic and mixed, with predominance of the inflammatory changes. In some portions of the white matter there were small focal areas of myelin loss, usually seen about small thrombosed veins. The nerve fibers, as well as the glia, were severely damaged or completely destroyed. The gray matter revealed no inflammatory or hemorrhagic changes and appeared fairly well preserved except for a mild degree of edema, associated with diffuse, ischemic alteration of the cells. In cases in which the cerebellum and the spinal cord were examined these changes were inconspicuous.

In the cases reported in this series a pyogenic infection was the primary etiologic feature, with the meningococcus responsible in 4 cases, the pneumococcus in 2 cases and a neisserian diplococcus in 1 case.

Scheinker, in view of the predominant involvement of the white matter and the association of the lesions with purulent leptomeningitis, designates the disorder as a meningoleukoencephalitis.

GUTTMAN, Philadelphia

STUDIES ON DEVELOPMENTAL PATHOLOGY. III. DISINTEGRATION IN THE NERVOUS SYSTEM OF NORMAL AND MALDEVELOPED EMBRYOS. PETER GRUENWALD, J Neuropath & Exper Neurol 4 178 (April) 1945

Gruenwald reports his observations on changes in microscopic structure in the brain of chick and human embryos which are called "disintegration." Essick originally observed areas in which clefts appear between the cells of the mantle layer in the corpora striata of the human embryo in the second month. In the same area in older embryos cysts were seen which had apparently developed by fusion of the clefts. These cysts are thought to occur in all normal embryos, are not artefacts and disappear completely when the embryo reaches a length of about 24 mm. Hochstetter confirmed and extended Essick's observations. He found that cavities appear again in the corpora striata after the disappearance of those described by Essick. He also observed large cysts in the cerebellum of embryos of 26 to 50 mm and smaller cysts in the diencephalon. Both authors found similar cysts in some mammals and failed to find them in others.

Gruenwald's studies confirm these observations. His studies show that in certain areas and stages of development of the embryonic brain there are peculiar changes in histologic structure resulting in the formation of clear spaces. Gruenwald calls this phenomenon disintegration and states that in many instances it leads to cyst formation. The changes appear in human and in chick embryos in various derivatives of the forebrain, particularly in the corpora striata and near the ventricular surface of the thalamus. Human embryos also show extensive cyst formation in the cerebellum. Gruenwald states that all these changes disappear completely. Similar disintegration and cyst formation were observed in or near malformed parts of the nervous system of chick embryos, in locations where disintegration does not occur normally.

Theoretically, there are several pathologic conditions that may arise from disintegration. In its normal location the disturbance may persist, probably because of an abnormal intensity or extent of the embryonic changes. In abnormal locations disintegration as such is pathologic but may be transitory. It is possible that disintegration may not be permanent but may persist long enough to disturb further development, and it is extremely difficult to predict possible consequences.

The presence of abnormal disintegration in the vicinity of gross malformations indicates that the abnormality extends beyond the gross anatomic disturbance,

either as its sequel or as a primary process This should be considered in evaluating the extent to which a maldeveloped nervous system may be histologically and functionally disturbed

GUTTMAN, Philadelphia

HEAD TRAUMA CAUSING REACTIVATION OF THYROTOXICOSIS, APPEARANCE OF DIABETES MELLITUS, AMENORRHEA AND MELANODERMIA LUIZ CAPRIGLIONE and JOSE SCHERMANN, *Arq de clin* **1** 311 (Sept) 1945

Caprighione and Schermann report the case of a white woman aged 36, the mother had diabetes mellitus and a sibling epilepsy There was a history of thyrotoxicosis following childbirth ten years previously, this had subsided with conservative treatment Six months before admission she was in a bus accident and lost consciousness There was no report of a fracture Soon afterward, polydipsia, polyuria and vulvar pruritus appeared She began to lose weight, became nervous, and tremors of the hands appeared Pigmentary changes were observed Clinical examination showed an enlarged, nodular thyroid, a small, atrophic uterus and diffuse melanoderma Her blood pressure was 110 systolic and 70 diastolic in the lying position and 100 systolic and 60 diastolic in the sitting position The basal metabolic rate was +22.5 and +34 per cent on two occasions The blood sugar measured 250 mg, the sodium, 350 mg, and the potassium, 25 mg, per hundred cubic centimeters The blood count was normal Biopsy of the skin showed abundant melanin pigment in the histiocytes of the skin Estrogens in the urine measured 100 and 800 units in twenty-four hours The authors believe the head trauma caused changes in the diencephalohypophyseal region, resulting in exacerbation of thyrotoxicosis due to hypersecretion of thyrotropic hormones The diabetes mellitus is considered a result of the effect of the hypothyroidism on the pancreas already affected by the previous bout of thyrotoxicosis The amenorrhea is said to be due to uterine atrophy induced by prolonged hyperthyroidism The diffuse hyperpigmentation results from stimulation of secretion of intermedin, also a sequel of the head trauma

SAVITSKY, New York

## Psychiatry and Psychopathology

INSULIN SHOCK TREATMENT AFTER SEVEN YEARS EARL D BOND and THURSTON D RIVERS, *Am J Psychiat* **101** 62 (July) 1944

Bond and Rivers reviewed the results of insulin therapy in 251 schizophrenic patients, 138 of whom were recovered or showed improvement at the end of treatment Forty-nine were followed for five years, and 22 of these maintained their improvement or recovery The spontaneous recovery rate in a control group was 16 per cent at the end of five years Of the 138 patients who demonstrated improvement at the last follow-up observation, 88 maintained their status and 25 had had a relapse, which persisted

Bond and Rivers point out the notably higher rate of recovery in the insulin-treated group than in the control group They are of the opinion that the quality of the remission in insulin-treated patients is of much higher standard than is the spontaneous recovery

FORSTER, Philadelphia

THE EFFECT OF ELECTRIC SHOCK THERAPY UPON CEREBROSPINAL FLUID PRESSURE, PROTEIN AND CELLS JAMES S L JACOBS, *Am J Psychiat* **101** 110 (July) 1944

Jacobs studied the alterations in the pressure, protein content and cell count of the cerebrospinal fluid induced with electric shock therapy administered to 21 psychiatric patients Occasional alterations of pressure were noted, and these

could be correlated with the patient's psychomotor status. Only in 1 patient did the author note a significant alteration in the protein and the cell content. The highest cell count for this patient, who had diabetes, hypertension and arteriosclerosis, was 28 cells per cubic millimeter, and the greatest total protein was 52 mg per hundred cubic centimeters. Jacobs concludes that the protein and cell contents of the cerebrospinal fluid should be determined prior to administering electric shock to patients with significant arteriosclerosis or hypertensive vascular disease.

FORSTER, Philadelphia

INSULIN, CARDIAZOL [METRAZOL] AND ELECTROSHOCK TREATMENT IN PALESTINE DURING THE LAST FIVE YEARS. KURT BLUMENTHAL, *J Nerv & Ment Dis* **101** 332 (April) 1945

Blumenthal discusses the theory and rationale of the shock therapies, particularly as applied to schizophrenia. He does not agree with Sakel's belief that the nucleus of the psychosis is being attacked but feels that the hitherto impenetrable wall about the nucleus is being penetrated. He feels that shock therapy "is a brutal and irrational intervention with an attendant therapeutic effect," and that in order to place the procedure on a scientific level the main efforts should be directed toward finding and isolating this therapeutic factor. With insulin shock it is the period of coma which is responsible for the therapeutic effects, and, according to Koppers, this is caused by the exhaustion of the sugar reserves in the interior of the nerve cells. During the first phase of insulin coma the blood sugar falls, while the intracellular sugar is enriched. At the first "turning point" of Georgi the potential difference has reached its maximum, the cell wall no longer holds, and the intracellular sugar flows through the broken cell walls into the blood stream. The turning point is a phase of enhanced irritability, when the so-called early epileptic seizure may occur. During the second phase the level of the blood sugar is rising while that of the spinal fluid sugar falls, and sugar impoverishment of the brain cells continues. In the metrazol-produced convulsive seizure, similar changes in the sugar content of the blood, spinal fluid and intracellular tissues occur, but in a matter of minutes rather than of hours, as with insulin. The effect of daily insulin coma or convulsive treatments is to increase the permeability of the blood-spinal fluid barrier. If the cause of schizophrenia is presumed to be an unknown toxic agent which causes a reactive "condensation" or decreased penetrability of the blood-brain barrier, then this action of the shock therapies in increasing permeability would be effective in a normalizing manner, since the "condensation" continues after the toxic agent has been eliminated and causes metabolic damage and secondary irreversible damage to the brain.

Of 267 patients with schizophrenia treated since May 1937, 26.43 per cent had full remissions, 28.10 per cent, social remissions, and 25.47 per cent, no benefit. The results were better in patients with early stages of the disease, in those with acute onset and in those with considerable affective component. A combination of insulin coma and convulsive therapy was more successful than either alone, although insulin coma was superior to convulsive therapy. A disadvantage of the convulsive method is the severe loss of memory, which may be responsible for an apparent cure when the patient has actually only temporarily forgotten his delusions.

CHODOFF, Langley Field, Va

MORBIDITY AND MORTALITY OF PATIENTS WITH PSYCHOSIS DUE TO CEREBRAL ARTERIOSCLEROSIS. O. J. POLLAK, *J Nerv & Ment Dis* **102** 27 (July) 1945

In a series of 2,000 cases in which autopsies were performed at the Taunton State Hospital during the past two decades, the clinical diagnosis of psychosis with cerebral arteriosclerosis had been made in 476. In only one fourth of the latter was death due primarily to arteriosclerosis. The average age at death was 71.

years In contrast to these findings, for other types of mental disease the mortality rate from arteriosclerotic processes was much lower (8 per cent), and, except for the senile psychoses, the average age at death was lower

CHODOFF, Langley Field, Va

BRAIN WAVES AND CLINICAL FEATURES IN ARTERIOSCLEROTIC AND SENILE MENTAL PATIENTS W T LIBERSON and C A SEGUIN, *Psychosom Med* 7 30 (Jan) 1945

Liberson and Seguin analyzed the clinical symptoms as related to the electroencephalographic pattern in 53 patients with cerebral arteriosclerosis or senile psychosis The electroencephalographic records were separated into extremely abnormal, intermediate and approximately normal groups About a third of the patients showed an extremely abnormal pattern, while another third presented no definite abnormality The patients were then grouped according to their major symptoms, and for each group the percentages of tracings belonging to the various electroencephalographic categories were determined In the group of patients with highly abnormal records confusion and irritability were more prominent, whereas in the groups with normal and borderline patterns agitation, anxiety and delusions were the most prominent symptoms Hallucinations and depression showed about the same relative values for the extremely abnormal, intermediate and approximately normal electroencephalographic groups

WERMUTH, Philadelphia

BRAIN WAVES AND HEREDITY IN MENTAL DISEASES W T LIBERSON and C A SEGUIN, *Psychosom Med* 7 35 (Jan) 1945

Liberson and Seguin studied the importance of hereditary factors in the determination of the electroencephalographic patterns of 118 patients with mental disease between 13 and 23 years of age The electroencephalograms were classified according to the degree and kind of abnormality present, and the patients were grouped according to the presence and importance of the abnormal hereditary factors in the family history The authors found relatively more patients with normal electroencephalograms in the group with a negative family history for mental disease than in the group with a positive history

WERMUTH, Philadelphia

DIFFERENCE IN THE MENTAL REACTION BETWEEN CHILDREN SUFFERING FROM CEREBRAL AND CEREBELLAR TUMORS LEO M DAVIDOFF, *Psychosom Med* 7 38 (Jan) 1945

Davidoff, over a period of twenty years, observed that children with tumors of the cerebellum seem to be unusually alert and cooperative and to have sweet dispositions A review of hospital records of about 50 children with cerebellar tumor appeared to bear out this impression A group of 20 children with supratentorial tumors, on the other hand, behaved in the manner usually expected of severely sick children

WERMUTH, Philadelphia

THE RELATIONSHIP OF ANTI-SOCIAL TRAITS TO THE ELECTROENCEPHALOGRAM IN CHILDREN WITH BEHAVIOR DISORDERS JOSEPH J MICHAELS, *Psychosom Med* 7 41 (Jan) 1945

Michaels found a high incidence of stealing and sexual misbehavior in a series of 122 children with behavior disorders Enuresis was associated in a positive manner with all the antisocial traits Analysis of the electroencephalograms of these children revealed that fire setting was the only sociopathic trait that was associated in a positive manner with electroencephalographic abnormality Enuresis, a psychobiopathic trait, also was positively associated with the abnormal electroencephalogram

WERMUTH, Philadelphia

RESULTS OF SHOCK THERAPY EVALUATED BY ESTIMATING CHANCES OF PATIENTS  
REMAINING IN HOSPITAL WITHOUT SUCH TREATMENT L S PENROSE  
and W B MARR, J Ment Sc 89 374 1943

Penrose and Marr described a new statistical method in shock therapy, the essence of which is a comparison of the actual number of shock-treated (insulin, metrazol) patients remaining on the hospital books at a given time with the expected number calculated from a random sample of the mental hospital population. Discharge, rather than probation, was taken as the index for the comparison of treated and control patients. The two groups were matched according to sex, age on first admission and lapse of time since the first admission. There is clear indication that fewer shock-treated patients remain on the hospital books than are to be expected from considerations of the control sample. An improvement attributable to shock treatment in the patients' conditions is implied, this is slight in cases of schizophrenia but pronounced in cases of manic-depressive and involutional psychosis.

KATZ, Boston

### Treatment, Neurosurgery

RECONSTRUCTION OF THE FACIAL NERVE A C FURSTENBERG, Arch Otolaryng  
41 42 (Jan) 1945

Furstenberg believes that the facial nerve should be preserved in operations on the parotid gland. It is possible and practicable to remove the entire parotid gland with preservation of the critical fibers of the seventh nerve. Careful and painstaking delineation of the nerve fibers, which may be identified with a light faradic current, frequently leads to excellent results. Removal of an infiltrating tumor of the parotid gland is compatible with preservation of the nerve. An optimistic point of view with regard to safeguarding the nerve can best be maintained by an initial exposure of the trunk near its emergence from the stylomastoid foramen. Thus early identification of the nerve is made possible, and its important ramifications may be traced with facility throughout the parotid gland.

In cases of traumatic injuries of the facial nerve an end to end anastomosis should be used when practicable. This is predicated on the assumption that the nerve has been severed by a clean cut or that only a small part of it has been damaged. Grafting may be the only method possible when large portions of the facial nerve have been destroyed. This entails, however, two points of union and thus doubles the hazard of fibrous connective tissue encroaching on the joints. In carrying out end to end anastomosis, the tortuous route of the facial nerve can be appreciably shortened by lifting the nerve out of its bony canal and freeing it along its course in the parotid gland. A union of the ends of a severed nerve which at first seemed futile may often be accomplished with this method.

RYAN, Philadelphia

EARLY REPAIR OF NEURAL WOUNDS WITH PENICILLIN THERAPY NATHAN C.  
NORCROSS, Arch Surg 50 67 (Feb) 1945

War injuries of peripheral nerves should be repaired as early as possible in order to obtain a good functional result. This can be successfully accomplished with the help of penicillin therapy. Patients with apparently clean wounds were given 10,000 units of penicillin every three hours from the second preoperative to the eighth postoperative day. To patients with infected wounds 20,000 units of penicillin was administered every three hours from the fourth preoperative to the tenth postoperative day, or longer. In all cases the wounds healed by first intention without complications.

LIST, Ann Arbor, Mich

PENICILLIN TREATMENT OF NEUROSYPHILIS A S ROSE, Connecticut M J 9 522  
(July) 1945

During the past fourteen months the neurosyphilis service of the Boston Psychopathic Hospital has treated 140 patients with symptomatic neurosyphilis. The treatment consisted of one half the usually prescribed amount of fever therapy and injections of penicillin, given concurrently or in succession. Sodium penicillin dissolved in saline solution was administered intramuscularly for a total dose of 3,000,000 Oxford units. According to Rose, penicillin is an active therapeutic agent in all forms of neurosyphilis, but the degree of effectiveness has not been determined. The best results are obtained with syphilitic meningitis. A small series of patients with primary optic nerve atrophy have shown surprisingly good results. All forms of parenchymatous neurosyphilis apparently need fever therapy as well as penicillin. Penicillin is an agent which acts directly on the invading organisms and therefore can be useful only in cases in which there is evidence of spirochetal activity.

J A M A

INJURIES TO THE CENTRAL NERVOUS SYSTEM WINCHELL MCKENDREE CRAIG,  
J Nerv & Ment Dis 101 451 (May) 1945

The treatment of closed and open injuries to the head has been improved since the effect of anoxia produced by trauma and inadequate breathing has been understood and a clear airway provided by placing the patient in the prone position, so that the tongue may fall forward and the saliva and vomitus escape. The use of oxygen not only has relieved anoxia but has helped to reduce increased intracranial pressure. Cerebral edema has been combated by the administration of plasma and serum albumin.

In this war infected head wounds have been a rarity, owing to the use of sulfonamide drugs and penicillin. Careful surgical debridement has been aided by the use of electrocoagulation and suction, and hemostasis, by the use of fibrin foam. The repair of defects in the skull with autogenous bone or cartilage or with alloplastic materials, such as vitallium, lucite or tantalum, has been much improved.

CHODOFF, Langley Field, Va

ELECTROCONVULSIVE THERAPY OF ACUTE HYSTERIA FRED FELDMAN, SAMUEL  
SUSSELMAN, BASILE LIPETZ and S EUGENE BARRERA, J Nerv & Ment  
Dis 102 498 (Nov) 1945

The authors report 2 cases with acute hysterical manifestations in which the results of electric shock therapy were successful. The first case was that of a white woman aged 29 who had generalized tremors and inability to walk following an automobile accident eighty-five days previous to admission. She failed to improve significantly after eight sodium amytal interviews and exhibited a new symptom—belching of air. Electroconvulsive therapy was instituted, and the patient showed rapid improvement and was discharged after nine treatments. The second case was that of an amnesic young woman, who also failed to respond to sodium amytal narcoanalysis. On the fourth hospital day she was given an electrically induced convulsion, which was followed within five minutes by the beginning of progressive improvement of memory.

CHODOFF, Langley Field, Va

COMPOUND CRANIOCEREBRAL INJURIES W J GERMAN, B S BRODY, and S C  
HARVEY, Surgery 16 874, 1944

German, Brody and Harvey reviewed a series of 64 cases of compound cranio-cerebral injuries. Sixty of the patients were operated on, the remaining four died within one and a half hours of admission, before preparations for operation could be

completed. The general policy of therapy was as follows: (1) immediate treatment of shock, (2) inspection, but not palpation, of the wound, (3) roentgenographic examination to reveal the extent and type of the fracture, and (4) operation within six hours for all patients surviving a preparatory period of two hours. The surgical principles employed were: (1) local anesthesia, (2) thorough debridement of the scalp, cranial wound and devitalized brain tissue, (3) removal of in-driven fragments of bone and foreign bodies, (4) closure of the dura, if possible, and (5) tight closure of the scalp. All patients (14 per cent) over 60 years of age died, their deaths forming more than 50 per cent of the mortalities in the series. Coma was generally a grave prognostic sign, nevertheless, more than one-third the patients arriving in deep coma survived. It does not seem that one is warranted in delaying operation for several hours in order to assess better the chances of the patient, at the same time increasing the possibilities of infection by delay. The authors agree, however, that when large numbers of battle casualties require urgent treatment the state of consciousness should be an important factor in selecting those with the more favorable outlook for early operation.

Shock should rarely delay operation beyond six hours, since modern methods of shock therapy are so effective and only the most severely injured will fail to respond in this time.

Operation was begun within six hours after the injury on all but 2 patients. Block removal of the compound scalp and cranial wound was done in 19 of the 52 patients whose wounds were not due to projectiles. The operative mortality rate was 26 per cent. This included the most severely injured patients. Excision of the scalp wound and removal of fragments from the cranial wound were done in 20 patients, including those with orbitonasal injuries, with an operative mortality of 10 per cent. Debridement of the scalp wound without removal of bone, chiefly for linear fractures without bone depression, was done in 13 patients, with an operative mortality of 77 per cent. The over-all operative mortality for those patients (52) without wounds due to projectiles was 15.4 per cent, and one-half these deaths were in patients over 60 years of age.

Primary closure of the scalp was done on all patients. Drains were inserted in the wounds of 29 of the 60 patients operated on. The dura was closed whenever possible.

In only 2 of 51 patients surviving six days did severe infections develop, and of these 2 patients, 1 died, a mortality due to infection of 2 per cent. Seven patients (14 per cent) had infections of the scalp, and only 2 of these occurred in persons for whom drainage had not been employed.

Nine patients had injuries due to missiles, and 6 of these (66.7 per cent) died. One of them died before operation could be performed. All 4 patients with traversing wounds died after operation. The total mortality rate for the entire series of 64 patients was 26.5 per cent, and the over-all operative mortality was 21.6 per cent.

SHENKIN, Philadelphia

#### ELECTROCOAGULATION OF GASSERIAN GANGLION K. H. BAUER, Chirurg 16 1 (Jan.) 1944

Bauer reports experiences with electrocoagulation of the gasserian ganglion in more than 500 cases of neuralgia. There was not a single fatality. Injection of solution of procaine hydrochloride is made to infiltrate the track for the puncture cannula to the base of the skull. A 12 cm. long, thin cannula, insulated with pyroxylin, is introduced and is passed slowly forward along the foramen ovale without touching the base. The passage through the foramen ovale is made manifest by sudden, radiating pain in the area of the third branch and by resistance offered by the nerve. Roentgenographic examination of the position of the needle prior to coagulation is imperative. Examination of the eyes is important because changes in vision, in the size of the pupils and in the ocular movements suggest that a change in the position of the needle is required. This may also be necessi-

tated by aspiration of blood or cerebrospinal fluid or by nausea. After these precautionary measures, high frequency electrocoagulation with the alternating current may be performed with the patient under evipal sodium anesthesia. Coagulation should be made in four stages, of fifteen, twenty, twenty-five and thirty seconds' duration. The intensity of the current is increased during the last stage. Coagulation itself should not be performed with local anesthesia. Residual pains may persist for two or three days. Electrocoagulation may be repeated when pain persists on the fifth or sixth day, as well as when there are recurrences. The advantage of the method is that the effect of the current is limited to the area immediately next the cannula, thus preventing severe destruction at the base of the skull or extensive sequestration of bone in the area of the base and of the upper jaw.

J A M A

ELECTROCOAGULATION OF GASSERIAN GANGLION BY THE KIRSCHNER METHOD  
B ODDSSON, *Acta psychiat et neurol* 19 293, 1944

In the neurosurgical department of Rigshospitalet, in Copenhagen, 86 patients with trigeminal neuralgia have been treated during the last six years with electrocoagulation of the gasserian ganglion by the Kirschner method. The location of the foramen ovale having been found percutaneously with an apparatus specially designed by Kirschner, the ganglion is punctured with a trocar, the stylet is removed, and a cautery probe is introduced, with which the ganglion is electrocoagulated. The operation takes a few minutes. The patients were between the ages of 19 and 92. There were 54 women and 32 men. The average duration of the neuralgia was six years, the longest period being thirty years and the shortest three months. The right side was affected in 55 patients and the left in 28 patients, and 3 patients had bilateral neuralgia, 74 patients had major and 12 atypical trigeminal neuralgia. Sixty-six patients had primary relief of symptoms, the remaining 20 having to undergo other treatment. The longest follow-up observation was fifty-one months, the shortest, three months. The follow-up observation revealed that 25 patients were relieved of pain and 7 were substantially improved, 13 patients had a recurrence, which in most cases yielded to a repeated electrocoagulation. There were no deaths. The best results, both as to primary relief of symptoms and as to prevention of recurrence, were obtained with trigeminal neuralgia of the third division. Oddsson suggests that most patients with major trigeminal neuralgia should be treated with temporal retrogasserian neurectomy. If the patient is not likely to stand the operation, injection of alcohol or neurexeresis may be carried out if the first and second divisions are involved, while with neuralgia of the third, and perhaps also of the second, division electrocoagulation of Kirschner should be performed. In special cases section of the sensory root alongside the pons by Dandy's subcerebellar route may be considered, but it seems likely that this operation will be superseded by the tractotomy of Sjöqvist, which has definite advantages.

J A M A



# Society Transactions

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## PHILADELPHIA NEUROLOGICAL SOCIETY

Walter Freeman, M D, *Presiding*

*Regular Meeting, Oct 26, 1945*

### Experimental Observations on the Use of Stainless Steel for Cranioplasty A Comparison with Tantalum DR MICHAEL SCOTT and DR HENRY T WALCIS

Stainless steel was used for cranial defects in 3 dogs, which were killed at the end of six weeks, three months and six months, respectively. The gross and microscopic studies made on these dogs showed that the stainless steel plates were completely encapsulated in every instance. There was no evidence of infiltration with polymorphonuclear leukocytes or round cells in any of the sections. There was no collection of serum above or below the plates. The reaction following the insertion of a stainless steel plate in the subdural space compared favorably with that reported by Pudenz and Odom following insertion of a tantalum plate in the subdural space.

Stainless steel plates were used in repair of cranial defects in 3 patients, but the follow-up period had been too short to warrant any conclusions.

It was concluded that the stainless steel plates compared favorably with tantalum plates used in similar locations. Stainless steel plates are easily obtainable and can be cut, shaped and molded at the operating table, and the price is approximately one-two-hundred-ninetyth that of tantalum. The authors believe that this material should be given a thorough clinical trial.

#### DISCUSSION

DR RUDOLPH JAEGER The problem of cranioplasty would seem at first glance to be a rather simple one. There is a hole in the skull, and it is to be filled with something or other. One would think one could take bone from here or there, or almost any noncorrosive metal that is not irritating, and fill the opening without the need for profound thought on the matter.

It is evident from a review of the surgical literature that cranioplasty must present a weighty problem in neurosurgical technic, because a great deal of thought has been applied to this procedure. I have felt that perhaps one single material should not be used exclusively for such repairs. The mental stability of the patient should be seriously considered when closing a defect in the skull. An older person whose mental reactions are well established will tolerate mentally almost any material one may wish to put into the skull. With the more nervous type of person, particularly one who has a tendency to a neurosis, one must think twice before putting a material like metal into a defect in the skull, where it will always show up in the roentgenogram. Almost certainly the patient will learn that it is there, and he may react mentally against its presence. I have felt that with this type of patient it is better to fill the defect with bone if it is possible. Once in a while the opening is so large one cannot find bone enough and must resort to metal or to Plexiglas.

Some years ago I started using stainless steel, soon after it was first advocated as a suturing material. I have closed a number of skull defects with it since I have followed the patients for a number of years, and in no instance have I found any signs of irritation or tendency to extrusion of the plate. I have used stainless steel many times in wiring the bone flap and in opening the wound for a second operation have seen the bright shining wire without any tissue irritation.

around it That is quite different from the reaction observed around a silver clip, where there is a blackened area of fibrosis, due to the oxidation and discoloration of the tissues

I should like to mention 2 cases in which stainless steel was used for cranio-plastic closure which are of importance in illustrating the tolerance of the cranial tissues to this substance In the first case a large bone defect remained in the frontal part of the skull after the removal of a huge area of hyperostosis and an underlying meningioma This was filled by a stainless steel plate, perforated many times and measuring 13 by 11 cm Six years later there were no signs of irritation from it, and the cosmetic result was excellent In the second case roentgenographic examinations and observations were made at frequent intervals for seven years This steel plate was much smaller (2 inches [5 cm] in diameter) There has not been the least sign of irritation from it

While I prefer closing defects of the skull with tibial grafts wherever possible I can see no reason that stainless steel is not fully as good as tantalum or other metals for this purpose

DR HENRY T WYCIS I want to thank Dr Jaeger for presenting these cases, because it gives one a little more confidence in knowing that one can leave these stainless steel plates in the skull for a long time without any untoward result

It is of interest that no matter what is put in the skull, particularly in the epidural space, one can hardly escape getting a reaction around it It is evident that all these plates were surrounded by a capsule, even though wired in the epidural space, so the plate certainly reacts as a foreign body

#### The Adult or Late Form of Amaurotic Idiocy DR N W WINKELMAN

An Irishman aged 25, with a history of convulsions from the age of 17, was brought to the hospital in status epilepticus He was confused and maniacal His temperature began to rise, and death occurred four days after his admission

Pathologically no gross lesions were encountered Histopathologic examination disclosed cells typical of amaurotic idiocy (the so-called Schaffer cell process), in groups or singly, scattered throughout the entire cerebrum, but especially in the cornu ammonis and the subthalamic area In the few cases reported in the literature the cerebellum has been particularly involved, and the spinal cord to much lesser degree

No well defined clinical syndrome can be given in view of the wide variability of the clinical pictures in the few cases reported

The age of onset of the condition, the clinical picture, which does not fit into any of the three types previously described, and the presence of the ballooned-out cells of the Schaffer type, singly or in groups, throughout the entire nervous system, but especially in the cornu ammonis and the subthalamus, justifies the placing of this case into the most recent subdivision of amaurotic idiocy established by Kufs and called by him the adult form of that disease

#### DISCUSSION

DR JOSEPH YASKIN What areas showed the late pathologic changes?

DR GEORGE D GAMMON What does autopsy show in other organs in the body in these late cases of amaurotic idiocy? Has there been any infiltration of fat elsewhere, as in the liver or spleen?

DR FREDERIC H LEAVITT I believe the infantile form is supposed to be more prevalent in certain types of people Is this condition looked on as a developmental defect, a degeneration or a possible infectious state?

DR N W WINKELMAN In answer to Dr Yaskin's question as to the location of the process While it was widespread and irregular, it involved the cornu ammonis and the subthalamic area to a greater degree than the rest of the central nervous system

In answer to Dr Gammon's question A complete study of the organs of the body failed to disclose any unusual changes, although in Kuf's second case a marked terminal disturbance of the lipid metabolism was observed in all organs

As to Dr Leavitt's question, I want to stress that at no point was there even a suggestion of an inflammatory process. It is likely that the process is a heredo-degenerative one, as Schaffer himself interpreted the condition. It is to be emphasized that the first reports of Kufs described the same condition in a sister and brother. The twin brother of my patient, who died in infancy of a cerebral condition, may have had a similar condition. Unfortunately, no autopsy was done.

From the report by Kufs, it is likely that these cases also belong to that group in which disorders of lipid metabolism have been found.

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Robert A. Groff, M.D., Presiding

Regular Meeting, Feb 22, 1946

**Vital Staining of Experimental Brain Abscesses** DR PHILIP P. GOLAND  
(by invitation), DR HENRY A. SLOVITER (by invitation) and DR FRANCIS  
C. GRANT

It has previously been demonstrated that when injected intravenously basic dyes stain the intact brain, whereas acid dyes, such as trypan blue, do not stain the uninjured brain. A number of workers have shown that when an acid dye is injected into an animal whose brain has been injured the dye tends to accumulate around the site of the lesion because of the local breakdown of the blood-brain barrier, whereas the remainder of the brain remains unstained.

In the present work, several azo and triarylmethyl dyes were synthesized and tested. One of these, an acid monazo dye, gave good staining and had the necessary requirements of low toxicity, good color stability, solubility and ready elimination. This new dye is the sodium salt of *p*-bromobenzene-azo-2-naphthol-3, 6-disulfonic acid.

The technic used for the production of brain abscesses in dogs was essentially that of Markley (*Proc Soc Exptl Biol & Med* 47:171, 1941). The best results were obtained by operation in the frontal region. Two days after injection of bacteria, 0.1 Gm of dye per kilogram of body weight was injected intravenously as a solution in 5 per cent dextrose. In most cases a second, similar, dose was administered after one or more days.

Postmortem examination of the brains of 26 dogs so treated revealed the following conditions: 1. In 13 brains acute abscesses developed, and 11 of these showed definite staining of the region surrounding the abscess. The grossly necrotic brain and the brain with acute encephalitis showed staining, the pus in the abscesses did not seem stained. 2. Six brains showed agar plugs with minimal reaction, and 5 of these were stained. 3. In 3 brains ventriculitis developed and in all the ventricular walls were stained. 4. In 4 brains meningitis developed, and no staining of pus or the leptomeninges was obtained. In no case was staining of the uninjured portions of the brain observed. Color photographs of some of the brains containing stained abscesses were shown.

Since the dye described contains a bromine atom, it is possible that introduction of a radioactive isotope of bromine may make it useful as a radioactive tracer. Further investigation of this possibility is now being made.

DISCUSSION

DR FRANCIS C. GRANT: The possible importance of the results that Dr Sloviter and Dr Goland have obtained lies in the possibility that these findings may facilitate the localization of a cerebral abscess. The selective staining of an infectious process might greatly improve the chances of its accurate identification.

after exposure of the suspected area. There is much work yet to be done, including of course the all-important first step of determining the toxicity of this material in man.

DR BERNARD J. ALPERS: This is an interesting paper. There is just one question that I should like to ask in relation to this study. It is known that if a vital dye is injected into the area of damage to the brain the dye is taken up by microglia cells particularly. This has been shown in an effort to determine whether the microglia cells were a part of the reticuloendothelial system.

It seems to me that the injection in the brains reported must be indicative of destruction of the brain tissue caused by the original experimental procedure and that it may have nothing to do with the process of the brain abscess itself. I wonder whether the authors have any observations on the type of cells that take up this dye. If it is the microglia cells, these observations would have relatively little application to the human brain, for the infiltration around cerebral abscesses is hematogenous.

DR PHILIP P. GOLAND: We have been going over the sections with Dr. N. W. Winkelman and we have not as yet determined which type of cell takes up the dye. We are going to make sections in which we do not use counterstains, such as hematoxylin and eosin. We are going to mount some sections unstained and see whether we can find particulate dye matter in them.

In connection with infections outside the brain there have been some studies with dyestuffs, and it has been shown that cells of the granulomatous reaction types will hold certain vital dyes. Macrophages and fibroblasts pick up these dyes, and the dye can be seen within these cells in granular form. The macrophages have a greater power of storing vital dyestuffs, but these deposits are less permanent than the more minute deposits in the fibroblast cells. It is possible that in chronic abscesses of the brain the fibroblasts may pick up the dye and hold on to it for a long time.

#### Reversibility of Dilatation of Cerebral Ventricles DR HENRY A. SHENKIN and DR CHARLES R. PERRYMAN

Three cases were reported of internal hydrocephalus caused by an obstructing lesion in either the third or the fourth ventricle which had been studied ventriculographically before and after relief of the obstruction. In every case the lateral ventricles were smaller after operation. It is believed that ventricular size is reversible in many instances if the dilatation of the ventricles is due to an obstructive lesion and the obstruction has not been present too long.

#### DISCUSSION

DR ROBERT A. GROFF: The data presented by Dr. Shenkin are very interesting. I was of the opinion that after relief of intracranial pressure, especially that resulting from tumors of the posterior fossa, the ventricles tend to return to a relatively normal size. These studies seem to bear out this opinion, or at least to show that the dilatation does not continue.

Two questions came to my mind during the presentation. Were the fluid contents of the ventricular system compared in the two examinations made on each of the patients? Why was a ventriculoencephalographic examination done as the second procedure on 2 of the patients since it does not permit a true comparison?

DR JOSEPH C. YASKIN: I am not sure, Dr. Groff, whether the findings in air studies can be regarded as conclusive proof of either the relative size of the ventricles or of cerebral atrophy. I believe that it is open to doubt in this case even though Dr. Shenkin used accurate, comparable technics with respect to the amount of fluid withdrawn and air introduced, the exposure, etc. Moreover, a study of 3 cases, even though absolutely accurate, is not completely convincing as to reversibility.

DR CHARLES R PERRYMAN I am not sure whether it was Northfield who in studies on cadavers pumped large amounts of air into the ventricles and was not able to demonstrate a sufficient change in the size of the ventricles to make distention a significant factor This, of course, was in the cadaver, and not in the living patient The neurophysiologic aspect is probably the most interesting, and we did not consider it in our discussion One wonders whether this enlargement of the ventricles, if it is not due to atrophy, could be the result of decreased fluid volume in the brain In other words, is there less subarachnoid fluid and a smaller blood volume, or is some other factor responsible?

DR BERNARD J ALPERS Is there any relationship between the duration of the hydrocephalus and the process of reversibility? Is it more likely that there will be reversibility when the hydrocephalus is acute than when it is chronic? Also, what is the functional interpretation of decrease in the size of the ventricle? Decrease in size of the ventricle need not indicate that function of the brain will improve, for good cerebral function is not incompatible with hydrocephalus It is seen with hydrocephalus of rather extreme degrees

DR H T WYCKS I merely wish to call Dr Shenkin's attention to a report in 1943 by Dr Jefferson Browder Dr Browder had shown a similar reversibility of dilatation of the cerebral ventricles following operation for subdural hematoma

DR HENRY A SHENKIN The duration of the symptoms in all 3 cases was short Onset preceded admission to the hospital by two to three months The tumors were all rapid growing

In the second case, in which there was the least reduction in size of the ventricles, the postoperative air study was done three months after operation, whereas in the first case it was done fourteen months after operation Another factor which may explain the difference in the degree of return to normal ventricular size is the age of the patient Our oldest patient, aged 38, showed less recovery than the other 2 patients, aged 8 and 18 years, respectively

The fluid was measured in each instance, but usually the initial study was ventriculographic and the follow-up study ventriculoencephalographic The amounts of fluid obtained, therefore, from the preoperative and the postoperative study were not comparable

Enlargement of the ventricular system with normal intracranial pressure is not infrequently found after cranial trauma It has been suggested that this is due to focal cerebral edema at the time of the injury, which causes a tentorial pressure cone and resultant block of the aqueduct of Sylvius, leading to internal hydrocephalus The ventricles are said to remain enlarged even after the causative mechanism has disappeared

Certainly, with the cases that we have shown tonight, this theory should be placed in some doubt, and other, more basic, changes in the cerebral hemispheres should be considered

**Effects of Denervation on Fasciculations in Human Muscle and Relationship Between Fibrillations and Fasciculations** DR FRANCIS M FORSTER, DR BERNARD J ALPERS and DR WINSLOW J BORKOWSKI (by invitation)

This article will appear in a future issue of the ARCHIVES

#### DISCUSSION

DR RICHARD MASLAND, Philadelphia It is important to emphasize the distinction between fibrillation and fasciculation In fibrillation the individual muscle fibers contract independently In fasciculation there is a synchronized discharge of a group of muscle fibers There is every reason to believe that this synchronization is due to neural activity and represents the response of a motor unit to a nerve impulse

It has been shown that in the case of the fascicular twitch which follows the administration of neostigmine there is a nerve impulse associated with the contraction This impulse may arise either through antidromic musculoneural trans-

mission or by direct stimulation of the nerve ending sensitized by the drug (Eccles, J C, Katz, B, and Kuffler, S W *J Neurophysiol* 5 211, 1942) When the nerve ending is stimulated, an antidromic impulse is set up, there is an axon reflex, and a motor unit discharge results

There is a striking similarity between the "neostigmine twitch" and the fasciculation of anterior horn cell disease Both are inhibited by small doses of curare The experiments just concluded indicate that each arises at the nerve ending It is my belief that in each instance the fundamental element is an abnormal excitability of the nerve ending

In attempting to explain the fact just demonstrated that although the disease is in the anterior horn cell the twitch arises at the nerve ending, it is important to bear in mind that the anterior horn cell includes not only the cell body but the peripheral nerve, which is its axon, and the nerve ending It is not remarkable, therefore, to discover that a disease which is demonstrated pathologically in the cell body within the spinal cord produces striking physiologic changes in the entire cell These manifest themselves as an alteration in excitability at one of the more highly specialized portions of the neuron—the nerve ending

DR BERNARD J ALPERS, Philadelphia I should like to say something in regard to the clinical significance of muscle fasciculations A sharp, cleancut distinction must be drawn between the physiologic origin of fasciculations and their clinical significance Physiologically, it seems to be true that the fasciculations occur as a result of some mechanism taking place at the myoneural junction

Dr Masland mentioned sensitization at the myoneural junction I should like to know what he means by sensitization, for it has been thought that fasciculations are fired off as a result of sensitization to acetylcholine All things considered, the evidence indicates that the physiologic mechanisms, whatever they are, take place at the myoneural junction, but one is still left with the clinical significance of fasciculations From this standpoint it seems still to be true that they are indicative of anterior horn cell disease We have made a number of observations on other patients with other conditions Fasciculations were found in a patient with severe disease of the cauda equina but not in another patient with a similar lesion They were also seen with serum neuritis and with ischemic neuritis In these conditions either there is associated anterior horn cell disease or the fasciculations may represent the result of retrograde changes in the anterior horn cell Fasciculations may occur in diseases other than those involving the anterior horn cell, but in my opinion many of the diseases which are reported as occurring with fasciculations without involvement of the anterior horn are in fact found to be associated with anterior horn cell disease This is true of infectious polyneuritis, which is said to occur with fasciculations very frequently, as well as of serum neuritis

I should like to raise the question of the significance of fasciculations in acute peripheral nerve disease May these not be the result of associated anterior horn cell disease?

DR RICHARD MASLAND, Philadelphia In reply to Dr Alper's question, Eccles has expressed the opinion that the increased irritability of the nerve ending observed with neostigmine poisoning may be due to prolonged negativity In view of the striking similarity between the twitch seen with such diseases as amyotrophic lateral sclerosis and the "neostigmine twitch," it is not unreasonable to postulate that the same factor is responsible for both

DR FREDERIC H LEWEY, Philadelphia The question of fibrillations or fasciculations is important also from the clinical point of view A review of the textbooks shows it to be almost an axiom that "fibrillation" is characteristic of a lesion of the anterior horn cell, in contrast to one of the peripheral nerve Oscillographic records show that the completely denervated muscle "fibrillates" This is not visible clinically The first sign of beginning reinnervation of a muscle is the appearance of not yet synchronized, spread potentials, which are now called "fasciculations" They are visible clinically as what were formerly called fibril-

lations No voluntary motion is possible at that stage The last stage of muscle reinnervation is characterized by the appearance of synchronized action potentials, i e, spikes, accompanied with the return of voluntary movements This experience gained from patients with peripheral nerve injuries corresponds to the observations of the authors, with the restriction that in diseases such as spinal progressive muscular dystrophy some units may be diseased and others still functioning well

DR FRANCIS M FORSTER, Philadelphia Our use of the term anterior horn cell should be clarified, for by that term we referred to the cell body and its nucleus, and not specifically to the axonal terminations The experimental data presented this evening indicate definitely that the impulses giving rise to fasciculations did not originate from the portions of the cells in the ventral horns of the spinal cord Fundamentally, I do not believe there is any real difference of opinion between ourselves and Dr Masland Our studies did not include patients with myopathies However, the myopathies are not always sharply delineated, and the occurrence of clinical or pathologic evidence of involvement of the cord with the myopathies is by no means rare

### PHILADELPHIA PSYCHIATRIC SOCIETY

O Spurgeon English, MD, *President, in the Chair*

*Regular Meeting, Nov 9, 1945*

**The Thematic Apperception Test Its Value in Routine Psychiatric Practice** DR HERBERT FREED, in collaboration with DR W F ECCER

The thematic apperception test is one of the projective techniques Whereas the Rorschach test has perhaps been the one of this group of tests most utilized, the thematic apperception test has a distinct advantage when one wishes to determine the content of a psychiatric disturbance rather than its form For this reason it can be used to facilitate therapy, since it often gives an immediate insight into the psychodynamics of the personality

The defects of the test were discussed, as well as its advantages, and 3 cases were used as illustrations

#### DISCUSSION

DR W F ECCER As a means of research, the patients were tested without the examiner's being familiar with their case records, in order to find out how well the test can determine features of the personality under evaluation Usually the test is carried out after some information about the patient is obtained, and the more one knows about the patient the more one can find out As a matter of fact, when the psychiatrist wants to find out anything specific about the patient, he indicates what he is seeking to the one administering the thematic apperception test

DR GERALD H J PEARSON This test is a good supplement and complement to the Rorschach test I suppose most psychiatrists of my generation at least are somewhat skeptical about tests as means of evaluating personality This skepticism is not entirely justified, as this test proves The diagnosis of the depth of the patient's illness cannot be made from the Rorschach test, whereas an evaluation of the content of his conflicts can be made with the thematic apperception test Thus one test complements the other

This test is useful in the diagnosis when time is limited, particularly in clinic work, or when a diagnosis has to be made rather quickly Some time ago I examined a number of children from an orphanage Orphanage children, particularly children who have been brought up from very early childhood in an institution, have a particular type of personality, which Anna Freud has described in her recent book, "Children Without Families" They have made

a good superficial adjustment. They get along well with other people, are bland, easy to manage, show little emotional reaction and say little about themselves. These children were all given a Rorschach and a thematic apperception test, and, as a result of the testing, it was found that a number who were apparently getting along nicely were actually extremely sick. These results show that if a rapid diagnosis is needed one can get a great deal of help from the thematic apperception test and the Rorschach test. Dr. Freed quoted Murray as saying that this test might be useful in psychotherapy. Anything that will help in getting significant material about the patient early is undoubtedly of value. Nevertheless, I see one or two dangers. If a psychiatrist gives the thematic apperception test in the beginning of psychotherapy and gets certain impressions about the patient from the test, he may tend, unless he is careful, to force the patient to produce material in psychotherapy which will substantiate the results of the test. Also, because he knows certain facts about the patient, he may tend to watch only for those facts and forget, or perhaps lose sight of, other intrapsychic currents of equal importance.

DR. MAX ROSSMAN, Allentown, Pa. From the way in which the material was presented, I felt that the thematic apperception test is a psychiatric technical tool rather than a psychologic test, such as an intelligence test. The thematic apperception test can be interpreted from three aspects—the literary quality, the emotional evaluation and the themes. From a diagnostic point of view, some awareness of the dynamics of the illness, of defense reactions and of emotional tone can be achieved by utilizing the thematic apperception test.

DR. H. CRAIG BELL. Could Dr. Freed tell us something about the technique of giving the test?

DR. WILLIAM FRANKLIN ECCKER. To determine the intelligence from the thematic apperception test is not an accurate procedure, but after the psychologist has given several thousand intelligence tests he can judge pretty well from the responses of the patient, from his handling of the vernacular and from his other behavior. However, this is not so reliable a way of getting some measure of the intelligence as is a regular intelligence test.

As for a description of the test, there are 30 cards. Ten cards are usually administered to men only, 10 to women only and 10 are given to both sexes. More recent developments in the test also include cards that can be given to children. It usually takes the patient about five minutes to make a story of two or three hundred words for one card, the entire test takes about an hour. If the examiner goes too far over the hour, the patient becomes tired, and the responses are not so reliable. Also, during the first hour the examiner gets acquainted with the patient. After he once has the patient's confidence, he can elicit much more material in the subsequent batch of 10 cards, which part of the test is carried out a few days later.

The cards are mostly of people. Most of them are of characters with whom the patient can identify himself. Some cards are of older persons, which the patient uses to identify with one or the other of his parents, and on other cards there are pictures which he can identify with other persons around him.

With regard to Dr. Rossman's comment, the test is a new one. It has not yet seen the development of the Rorschach test. Dr. Murray first published it in 1935, and it has not been subjected to much research, nor has it yet been standardized. The scoring procedure is not as complicated as that of the Rorschach test.

DR. HERBERT FREED. Something can be done in the way of diagnosis. We hinted at it in the paper. It will be found that one can often make a diagnosis of hysteria from the way the patient words her stories. Again, patients with compulsive neuroses will often not come to any one conclusion as to what the character does, their indecision in telling the story may become diagnostic. The same holds true with schizophrenia.

Perhaps I am too optimistic, but I think that in the future we shall have a different type of diagnostic classification. One will not depend on a label.



and say that this patient has schizophrenia but will say that he has certain dynamic trends which underlie his illness I think this test will have a great deal more to offer in the future

### Psychiatry and the Public MRS EDITH M STERN, Washington, D C

A layman would not presume to speak of psychiatrists' relations with patients but would speak only of their relations to the public Although the relation of psychiatry to the public improved during the war, full popular confidence is still lacking Advertising and publicity differ from public relations, the latter is concerned with the creation of attitudes Unfortunately, few psychiatrists are public relations minded By default, quacks flourish and psychiatrists tend to be consulted only in extreme need, not casually, preventively, as are pediatricians and ophthalmologists Laymen, even in high places, mistrust psychiatric competence, and journalists tend to misrepresent things psychiatric

There still exists a medieval hang-over in attitudes toward mental disorders, and psychiatry is viewed as new, vague and untested However, correction of much popular distrust is within the psychiatrist's control, without sacrifice of professional dignity or integrity A few suggestions are offered When writing for laymen, it is advisable to avoid the chance of confusion either with professional polysyllables or with concessions to loose popular terminology Sensational journalists should not exploit psychoanalysis at the expense of neglecting many other, briefer, more popularly comprehensible technics of psychotherapy Court decisions evidencing psychologic ignorance, and, above all, press, stage and screen distortions of psychiatry and psychiatrists should be protested

Public relations are a potent force, and psychiatrists are greatly needed, directly as physicians and indirectly as advisers, in all fields involving human behavior With this goal in view, the public's confidence must be deliberately cultivated by those concerned

### DISCUSSION

DR FREDERICK ALLEN I was privileged to read a brief extract of Mrs Stern's discussion and felt that the subject was important for this group to have discussed It is refreshing to get the reactions of lay people We psychiatrists need to know what others think of us It is clear that we do have a public responsibility to disseminate in a simple and direct way the knowledge of human nature that we gain from our professional work We have a responsibility to play a leading role in correcting ignorance and in creating a less prejudiced and more intelligent understanding of mental illness We should assume leadership in those educational programs designed to help the people in our community to view mental illness with less fear and anxiety I deliberately say less, rather than no, fear, because we are concerned with an area of professional practice dealing with problems in which the element of fear and anxiety is inherent There will always be anxiety aroused when persons need to consult a psychiatrist either about themselves or about members of their family The very nature of the problems for which they need help involves anxiety and fear When the step is taken with casualness, it frequently has little meaning It is not human to approach emotional problems without some feeling of fear being aroused But we can reduce through education and through sound clinical practice the amount of ignorance, the blind prejudice, that still exists about various types of emotional and mental disturbances This will apply particularly to cases in which it is necessary to place a patient in a hospital for the mentally ill

We can do a great deal more than we have done to create a more enlightened attitude about the place and function of hospitals for mental disease Right here in Pennsylvania we are confronted with a very real need of conducting a broad educational program to bring about more adequate support for psychiatric hospitals, in order to assist them to attain higher professional competence and to obtain broader clinical facilities for achieving it The institutions for the mentally ill are designed to heal, but many of these hospitals today are in no

position adequately to discharge this responsibility Too frequently they have become custodial places with relatively low professional standards The staffs of these hospitals are working under terrific handicaps, and they need our able and vigorous support to make them hospitals in fact, and not just in name

I liked the point Mrs Stern made concerning the tendency of psychiatrists to become dogmatic in their public utterances We have all, like Mrs Stern, heard public statements by psychiatrists that make us squirm In the field of child psychiatry, the field with which I am most familiar, there has been a strong tendency in public presentation to stress the pathology of parenthood This has been emphasized so much in the innumerable articles written and speeches made that the impression has been created that parenthood in itself is something of a disease Emphasis has centered too much on what was wrong with parents and not enough on what they can do, and are doing, to make their relations with children a healthier one We need to stress more our interest in understanding people as they are and in helping them gain from that basis a feeling of greater self respect and an increased capacity for responsibility We do not do this merely by pointing out and stressing all the mistakes that parents make It is this negative emphasis that we need to get away from Not long ago I heard a psychiatrist, in discussing the effect of fathers being away in military service, state that young boys in this generation are going to grow up to be abnormal because they have not had their fathers Such statements, it seems to me, are irresponsible and serve only to engender both antagonism toward psychiatry and fear of it

Mrs. Stern's presentation stresses the responsibility we have toward making psychiatry a more human and dignified professional field In the long run, that which will do the most toward achieving this end is sound clinical practice in our day to day work with our patients This in the long run will have much more influence than what we write in magazines or say on the public platform But if what we say and write can really spread and be based on sound clinical practice, then the lecture and the magazine article become important educational influences

This more negative emphasis has had an unfortunate application in many recent articles which have stressed the possible abnormalities of returning veterans Many people were encouraged to feel that the returning soldier was going to return to his community with a curious abnormality and a bundle of complications This stirred up a great deal of unnecessary and false fear and anxiety This has not been the psychiatrist's fault only, in fact, many psychiatrists, recognizing this unfortunate tendency, have done a good deal to correct it and to set in motion and bring out a different kind of literature

Psychiatrists work in a field that seems to lend itself to a great many forms of quackery Again, this is not the fault of the psychiatrist alone, some of the newspapers and magazines aid and abet this tendency by publishing crazy articles that dramatize something in human nature As long as there are unbalanced people to write such stuff, it seems possible, unfortunately, for them to find some one willing to publish it It is not always so easy or so attractive to dramatize the truth But we need not be too much discouraged, for there probably will continue to be curious samples of psychiatry written about in the press or dramatized in moving pictures We cannot correct all this, but we can perform our own jobs in such a way that people will gain in time a more enlightened attitude To contrast attitudes of today with those of ten or twenty years ago can give us courage, for we have come a long way There is still much to be done, however

There is just one comment of Mrs Stern's with which I cannot agree—her reference to getting other professional people to do our work for us, on the basis of our not having time ourselves This is not a fair description of the important contribution which the social worker has to make in this field I have never conceived of a social worker simply as a person to whom one can turn over a job, rather, I have felt that the contribution of these workers comes when we work with them on a professional basis We can learn a great deal from the

trained social worker who has a keen sense of her professional job and of the areas in which she operates

DR HOWARD K PETRY, Harrisburg, Pa From the point of view of state hospital work, the psychiatric patient seems almost to be the forgotten man, the friendless man We psychiatrists have not interested the public in the problem of the mentally ill Laymen are still afraid of such persons They still do not want to meet or associate with them It is still pretty difficult to get even a board of trustees in a psychiatric hospital to go around and see the details of the situation for which they are actually responsible

In the state hospital system, these conditions arise partly because we have moved inside a fence We have not lived with the people of the community We have had our social life within the fence, and one of the hardest things in the average state hospital is to get the staff to become part of the community and to get the community to know them

In our practical discussions we have not got down to the level of the Anglo-Saxon vocabulary in talking to the people I think psychiatric institutions have suffered, too, because they have had a bad background They grew up from the poorhouse and have not been able to escape their ancestry

I am convinced that as psychiatrists we must sell ourselves to our own profession as an initial step We must get the psychiatrist into the general hospital and must make the public see that there is no sharp dividing line between mental and physical disease The younger members of the profession have had better training, but the older ones are still hard to approach on this problem

DR ARTHUR P NOYES, Norristown, Pa I don't know that I entirely agree with Mrs Stern about protesting court decisions The remedy is probably one of education Perhaps it would be well if the law schools would send their students for a few weeks to the hospitals for mental diseases, just as the theological schools are beginning to send their students Nothing has contributed to a better understanding on the part of the clergy with respect to human motivations and mental hygiene than this procedure If the law students could receive training along the same lines, there would be a much better informed judiciary

DR HAROLD PALMER We have needed to talk over some of these things, and we are grateful to Mrs Stern for bringing up the subject for discussion I am tempted to say something in defense of the psychiatrists

Not long ago a famous agency sent an article submitted to them by an author to several Philadelphia psychiatrists The latter read the article and pointed out that it was unsound, sensational and inaccurate, but the article was published without a single change There are a number of such occurrences

I agree with Dr Allen that we ought to spend more time on the scarce material that has been published on neuropsychiatry during this war I wonder how many of you saw the bulletin called, "A Thousand a Day," which carried the statement, "A thousand screwballs a day released from the armed services" On the other hand, articles have appeared which counteract these destructive implications In an article which I have at hand it is stated that of 14,000 veterans who had returned to an industry which employed 130,000 people 29 per cent were neurotic discharges Now in that group the job turn-over was less than the average for the plant The output of a third of these neuropsychiatric discharges exceeded the average industrial productivity of the plant, and another third were working at higher skills than they were before they went into the Army

It may be recalled that 42 per cent of candidates coming up for induction were classified as neuropsychiatric Some interesting statistical work has been done on the actual percentage of neuropsychiatric cases in the services When the cases in military service were studied by the same standards as those in civilian life, it was found that the percentage of breakdowns was actually less when the same age groups were compared

I want to thank Mrs Stern for throwing light on this matter We needed it very much

DR SAMUEL B HADDEN I am sure that many of you were thinking of the words of the immortal bard of Old Scotland

"Oh wad some power the giftie gie us  
To see oursel's as otheirs see us"

We have had this opportunity The recent meetings conducted by the Philadelphia County Medical Society showed an average attendance of between 400 and 500 People are indeed interested in mental health, and if they do not get information from psychiatrists, they are going to get it from some other source

The serious problem is with the civilians who did not get into the service They are by far the more pathetic group, not the returning psychoneurotic soldiers

We have a contribution to make to better living, and our corrections might well begin in the schools and carry on from first grade, both with the students and with the faculties The public is interested, and we might as well give them the information, rather than have them get it from some commercial group which will capitalize on it

DR A H PIERCE If we are going to sell ourselves to members of the medical profession in general, we have got to do it in as straightforward Anglo-Saxon English as possible All have heard psychiatrists read papers at medical meetings which only mystified the average practitioner, yet it is perfectly possible to express one's ideas in simple English

After members of the medical profession have been sold on us in an understanding fashion, it will be easier to reach the public as a whole

MISS S O'HARA, Harrisburg, Pa I am particularly interested in Mrs Stern's emphasis on adequate public relations It happens to be one of my responsibilities as Secretary of the Pennsylvania Department of Welfare, to secure the understanding and the good will not only of the public generally but also of the officialdom of the state The construction of hospitals alone is not the answer to the problem of mental illness By that I mean that the public must realize the need for preventive methods I should like to keep patients out of hospitals for mental disease Members of the medical and the nursing professions and the public generally must become conscious of the need for diagnostic facilities and preventive psychiatric services in the average-sized community—for care on the part of the general practitioner in the early stages of mental illness

The need for the services of the psychiatrist is the first which the patient or his family should be conscious of wanting The need for psychiatric hospitals should follow long after, and I congratulate this society in recognizing the fact and in bringing into this conference a layman like myself to discuss the methods of informing the public

MRS EDITH M STERN, Washington, D C I welcome the improvements which have been made on my suggestions tonight I think that the idea of more psychiatric writing in popular magazines, instead of in your own journals, is excellent But it is not a question of writing about the sick mind, the angle should be that of mental health Also, I believe that it is an excellent idea to have law students go through hospitals for the mentally ill, that is what good public relations mean My suggestions do not stem from my own opinion of psychiatrists, they represent the unfortunate opinions which I have heard a variety of laymen express

Psychiatrists must not take the helpless attitude that the press is so terrible, that they cannot do anything about it They can It will not be done immediately, but, as I said originally, if psychiatrists do not encourage the reputable writers, the latter will dig their information out of the medical journals No doubt many unsound writers will still do that I think that Dr Palmer's suggestion is fine, to have a public relations committee to establish relations with various writers who can be trusted and to whom psychiatrists can safely give their material

Government agencies, of course, cannot come right out and refuse to give information to anybody, but they have subtle ways of withholding it from undesirable persons Psychiatrists can adopt the same policy about giving out or withholding their information

# News and Comment

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## RESEARCH POSITIONS CREATED

The Honorable S M R O'Hara, Secretary of Welfare of the Commonwealth of Pennsylvania, announces the establishment of twelve positions for research in psychiatry and related fields at the Western State Psychiatric Institute and Clinic, Pittsburgh. At the institute numerous clinical and teaching activities, the latter in collaboration with the University of Pittsburgh School of Medicine, have already been initiated.

The institute is the teaching and research hospital of the Pennsylvania mental hospital system, which includes twenty-one hospitals and institutions, with an average of 40,000 patients. Thus, access to much clinical material is assured. Here, it is expected will be trained psychiatrists, social workers, psychologists, nurses, occupational therapists and others for hospitals and private fields.

These new positions provide for the appointment of properly qualified senior and junior research workers in psychiatry, internal medicine, biochemistry, neuropathology, neurophysiology and clinical psychology. Several positions, as in psychology and neurophysiology, are currently filled.

In some instances research at the institute will be coordinated with teaching at the university, in such cases the applicant for appointment, and his qualifications, must meet also with the approval of the dean of the school of medicine.

Interested persons may obtain further information by writing to the director of the institute, Grosvenor B. Pearson, M.D., O'Hara and DeSoto Streets, Pittsburgh 13.

## AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY, INC

A meeting of the American Board of Psychiatry and Neurology, Inc., will be held in New York, Dec 16 and 17, 1946. Applications for examination should be completed and in the hands of the secretary by October 6. The December meeting is the last opportunity for the consideration of candidates who desire certification on record.

Dr F J Braceland, 102-110 Second Avenue, S W, Rochester, Minn., is secretary-treasurer, and the executive offices of the board are at that address.

## ASSOCIATION FOR RESEARCH IN NERVOUS AND MENTAL DISEASE

The Association for Research in Nervous and Mental Disease will meet jointly with the International League Against Epilepsy on December 13 and 14 at the Waldorf-Astoria Hotel in New York. The subject for discussion will be Epilepsy. Correspondence may be addressed to Thomas E Bamford Jr, secretary, Association for Research in Nervous and Mental Disease, 115 East Eighty-Second Street, New York 28.

## NINTH ANNUAL LOUIS GROSS MEMORIAL LECTURE

The ninth annual Louis Gross Memorial Lecture will be delivered under the auspices of the Montreal Clinical Society at the Jewish General Hospital, Montreal, on Wednesday, Oct 23, 1946, at 8 30 p m, by Dr Roy R Grinker, director of the Institute for Psychosomatic and Psychiatric Research and Training of the Michael Reese Hospital, Chicago. The subject will be "Psychiatric Objectives of Our Time."

## Book Reviews

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**Experimental Hypertension** By William Goldring, Richard J Bing, Eduardo Cruz Coke, W D Collings, L W Donaldson, M L Goldberg, Harry Goldblatt, B Gomberg, Arthur Grollman, C A Johnson, Oliver Kamm, Luis F Leloir, H Minatoya, W G Moss, Eric Ogden, Irvine H Page, John W Remington, L A Saperstein and G E Wakerlin Special Publications of the New York Academy of Sciences, R W Miner, Editor, Volume III Pp 180 New York, 1946

The collection of papers gathered into this volume indicates that an understanding of the mechanism of experimental renal hypertension is in the stage of apparently conflicting evidence and opposing views. The papers are those presented in February 1945 at a conference held by the Section of Biology, New York Academy of Sciences, on experimental hypertension and deal for the most part with the so-called renal hypertension experimentally produced. They make little attempt to correlate the evidence but offer the data and opinions of investigators who have explored various phases of the problem.

The renin-angiotonin system—its production and chemistry and the characteristics of its activity—is discussed, but “no conclusive proof [is] offered that it is in fact the cause of elevated blood pressure.” Dr Irvine H Page presents important support of the humoral pressor theory in demonstrating, on ear vessels of the perfused rabbit, a vasoconstrictor substance differing from angiotonin and present in the blood plasma of animals and man with hypertension. But Grollman, and Ogden and his associates find facts which seemingly cannot be reconciled with the humoral pressor mechanism. Grollman suggests that the operative procedure causes the absence of a substance normally produced by the kidney, and without which hypertension results, Ogden and his co-workers believe that in the production of chronic hypertension a neurogenic mechanism is important.

Whatever the theory, the facts of renal metabolism in hypertension must be explained. Raska (not mentioned in the list of authors) summarizes work on the oxidizing power and concentration of respiratory catalysts in the kidneys in renal hypertension, and Bing shows how the kidney in anaerobic states may produce pressor amines.

The work on renal antipressor extracts is difficult to correlate, largely because depressor properties are found in various fractions and because different laboratories yield such differing results. “It is generally thought that the effect of these extracts is non-specific.” An interesting action of Wakerlin’s extract in dogs is the protection of a small number of the animals from experimentally induced hypertension.

In short, the book presents what is known of experimental renal hypertension and indicates the direction of future investigation. The integrating effect of the conference which produced this book seemed much needed.

**Motor Disorders in Nervous Diseases** By Ernst Herz, M D, and Tracy J Putnam, M D Price \$3 Pp 192 New York Kings Cross Press, 1946

The development in the use of moving picture films for educational purposes has brought out a treatise appropriately entitled “Motor Disorder in Nervous Diseases,” by Drs Ernst Herz and Tracy J Putnam.

The work is composed of two parts, an “Atlas” in small textbook form and ten reels. The descriptive atlas intended for use in conjunction with the films, consists of some 180 pages and is, in a limited sense, a textbook. The work consists solely of an analysis of disturbances of pathologic conditions in the motor sphere. The

book contains elaborate and instructive material, clearly presented, of use both to the student and to the physician. The style, manner and form of presentation are such as to maintain the interest of the reader.

The films are finely executed. The subject matter is profusely illustrated in the book itself by strips from the series of films.

While the text and illustrations are devoted especially to the presentation of purely clinical features of motor disorders, the associated implications of anatomic and pathologic conditions are presented both from an investigative physiologic and from a chemical viewpoint. The relation between motor function and anatomic structure has been considered minutely in the elucidation of the clinical entities and elaborated in the book by means of drawings, both plain and animated.

In developing the various presentations, the authors show the experienced teacher's appreciation of the difficulties of the medical student in passing from the basic studies to his approach to the patient, and both the textbook and the films are an important aid in this part of the student's experience.

The authors have called on experts in special fields of related subjects to aid in elucidation of some of the subjects requiring special explanation, as, for example, in their outline of the physiochemical aspects of neuromuscular transmission, in their discussion of the visual mechanism as related to neurology and in their presentation of neuro-otology.

The following grouping gives an idea of the manner of presentation of the films. The first division deals with "Involuntary Movements in Nervous Diseases." The "Atlas" presents a study of the various types of deformities of movement, including athetosis, dystonic postures, chorea and myoclonus. The book contains excellent descriptions and analyses of these conditions. The film clearly demonstrates the descriptive material. The second film deals with disorders of gait, the third, with disturbances in coordination. One would have to study many textbooks to gather the information contained in the few pages on this subject. The fourth film, on muscle status, is an excellent study in disorders resulting from gross and fine pathologic processes of muscle, clinical demonstrations are ample. Of especial interest is discussion on neurophysiologic relations, including the reaction of acetylcholine. The fifth film, on reflexes, deals with clinical demonstrations and pathologic interpretation of the important reflexes. The sixth film, on skilled acts, consists in an analysis of incoordination, akinesia and abnormal involuntary movement, and the various types of motor pattern in eupraxia, apraxia, ideokinetic apraxia (Liepmann) and constructive apraxia (Kleist). In the seventh film, disorders of the ocular system are discussed in detail, with profuse illustrations. The eighth film deals with facial palsy, the ninth, with disorders of the vestibular system. The chapter in the book and the illustrative film constitute a complete study of disorders of the vestibular system, it gives methods of examination with minute elaboration of various tests associated with the pathology of this complicated mechanism. In the tenth film disorders of the motor part of the trigeminal, spinal accessory and hypoglossal nerves are illustrated, with presentation of patients and animated pictures of the anatomy and descriptive pathology.

This valuable contribution to current medical literature should have a wide distribution as a teaching medium. It will find a place in every institution for medical education.

## HISTOPATHOLOGY OF POLIOENCEPHALITIS HEMORRHAGICA SUPERIOR (WERNICKE'S DISEASE)

FRANK W. BAILEY, MD  
CHICAGO

THE CONDITION named polioencephalitis hemorrhagica superior by Wernicke<sup>1</sup> was considered by him to be largely, yet not entirely, due to alcohol poisoning. The symptoms are palsies of the ocular muscles, which finally lead to complete paralysis, reeling gait, vertigo, headache, nystagmus, optic neuritis, photophobia and disturbances of consciousness. The last-mentioned symptom may be characterized by drowsiness either from the onset or as a terminal state. External ophthalmoplegia may occur in varying degrees and combinations. Certain ocular muscles, such as the sphincter of the iris and the levator palpebrae, are usually unaffected. The pathologic process involves the origin of the upper cranial nerves but may extend to include the lower ones (polioencephalitis superior and inferior), resulting in bulbar paralysis. The disease follows an acute or a subacute course and usually ends in death in eight to fourteen days, but a more protracted course with ultimate recovery may occur. All 3 of Wernicke's original cases ended in death within a period of two weeks.

### THEORIES OF CAUSE

The mechanism by which the chronic damage to the nervous system by alcoholism in this disease comes about is no longer considered to be directly traceable to the alcohol itself.<sup>2</sup> Alcohol is not the unique cause, and its action in some instances may be secondary, yet the fact remains that the clinical and pathologic changes in this condition accompany not a few cases of chronic alcoholism. The trend of the explanation of the mechanism is away from the older assumption of a direct toxic action on nerve tissue of alcohol itself and, rather, toward

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From the Department of Anatomy of the University of Southern California, and the Neurological Service of the Presbyterian Hospital.

<sup>1</sup> Wernicke, C. *Lehrbuch der Gehirnkrankheiten*, Berlin, T. Fischer, 1881, vol 2, p 229.

<sup>2</sup> Alexander, L. *Neuropathology of Alcoholism*, *J Nerv & Ment Dis* 90:385, 1939. Campbell, A. C. P., and Russell, W. R. Wernicke's Encephalopathy (Polioencephalitis Hemorrhagica Superior). Its Alcoholic and Nonalcoholic Incidence. *J Path & Bact* 48:245, 1939.



a nutritional deficiency due to metabolic disturbances produced by the chronic ingestion of alcohol. These disturbances are due to neglect of proper diet by the chronically alcoholic person, incomplete absorption of vitamins from food due to gastritis and intestinal changes produced by alcoholism, and a condition of increased vitamin requirement due to the high caloric effect of alcohol.

#### NATURE OF THE PROBLEM

The purpose of this investigation was to determine the pathologic changes resulting from the metabolic disturbances produced by chronic alcoholic toxicosis, which develops after five to forty-five years of excessive alcoholism. There are two chronic clinical conditions, namely, alcoholic polyneuritis and alcoholic psychosis, each of which has its own characteristic lesions.

The pathologic process in polyneuritis is characterized by central and peripheral neuronitis, with swelling of ganglion cells predominantly in the motor and frontal cortex and the anterior horns of the spinal cord, followed by degeneration of the nerve fibers, particularly of the myelin sheaths, in the peripheral and central nervous system. This condition has been produced in animals by depriving them of thiamine and resembles the clinical condition of beriberi or pellagra.

The pathologic changes in alcoholic psychosis are characterized by small foci of degeneration and varicose deformity of vessels, proliferation of blood vessels and increase of the fixed cells of the vessel walls, subacute necrosis of the parenchyma and proliferation of the glia, with or without ring hemorrhages. The changes occur predominantly in the basal portion of the diencephalon, midbrain and medulla and in the periaqueductal gray matter at the level of the oculomotor nuclei. These lesions were first described by Wernicke<sup>1</sup> as *polioencephalitis hemorrhagica superior* and *inferior* and later by Bumke and Kant.<sup>3</sup>

There are two phases of the structural change of the latter condition to which further study and consideration may be given. The first is its interpretation in terms of known biochemical reactions, the other concerns the changes in the nerve cells and in the connective tissue of the brain, namely, the neuroglial elements.

#### MATERIAL

The material used in this study consisted of central nervous tissue obtained from 5 cases, the specimens of which had accumulated in the Cajal laboratory of the Los Angeles General Hospital. In each case there was a history of chronic alcoholism and the clinical symptoms and findings of Wernicke's *polioencephalitis hemorrhagica superior*. The clinical history and gross pathologic changes in the brain in each case are presented.

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3 Bumke, O., and Kant, E., in Bumke, O., and Forster, O. *Handbuch der Neurologie*, Berlin, Julius Springer, 1936, vol. 13, p. 852.

CASE 1—A white woman aged 52 had fainted three months previous to her admission and had not been clear mentally since that time. She was disoriented at times with regard to place and was said to have had convulsions on the day of entry to the hospital. The sister stated that the patient was chronically alcoholic. Her pupils were equal but not regular and reacted sluggishly to light and in accommodation. Her heart was regular and her lungs were clear. All reflexes were absent, and there was marked degeneration of the fundal vessels of the retina. Laboratory tests gave normal results. Two weeks after admission she died, with a temperature of 106.4 F, a pulse rate of 136 and a respiratory rate of 40 per minute.

Gross examination of the brain at autopsy showed that the convolutions of the central region were somewhat atrophied and the arachnoid somewhat thickened and opaque, indicating a slight chronic arachnoiditis with early cortical atrophy. Repeated sections of the whole brain showed no gross alterations and no areas of hemorrhage or necrosis.

CASE 2—A white male laborer aged 50 was admitted to the hospital with swollen ankles, weakness and anorexia, which he had had for several weeks. For five months his diet had been impoverished, and he had consumed at least 2 quarts (2 liters) of muscatel wine daily. His blood pressure was 85 systolic and 70 diastolic. There were moist rales in both lungs. Both ankles showed pitting edema. The routine laboratory tests gave normal or negative results. The electrocardiogram showed evidence of myocardial damage. The patient died fourteen days after admission.

Examination of the brain showed gross cortical atrophy with widening of the sulci. The blood vessels were small, thin walled and hypoplastic.

CASE 3—A white woman aged 46 entered the hospital with a history of chronic alcoholism and in a state of deep coma. Her pupils were irregular and unequal, the left being larger than the right. They were reactive to light. There was ptosis of both lids, more pronounced on the left. The left eyeball was fixed. Both optic disks were normal. There was slight weakness of the lower left side of the face. There was tremor of both hands and of the right leg. The extremities of the left side were weak. The deep reflexes were increased. The Babinski reflex was present bilaterally. The spinal fluid was slightly exanthochromic, and the Pandy reaction was 4 plus, a count showed 370 fresh red blood cells and 4 white blood cells per low power field. Her temperature ranged from 99.8 to 101.0 F, and she remained comatose. Twelve days after admission she died.

Gross examination of the brain showed no external markings. Repeated sections of the brain showed multiple small hemorrhages in the brain stem and periaqueductal region, with blood in the aqueduct. There were small hemorrhagic spots in the thalamus, the cerebral peduncles and the subthalamus and one in the medial nucleus of the right thalamus.

CASE 4—A white man aged 69 entered the hospital with a history of chronic alcoholism and hemiplegia on the right side, which had developed during the past year. After his admission he became confused and incontinent. He was emaciated, and his tongue was red. He breathed rapidly and swallowed with difficulty. There were rales at the base of both lungs. His heart was enlarged to the left, and its rhythm was irregular, with extrasystoles. His blood pressure was 95 systolic and 60 diastolic, and his heart rate was 102. The only neurologic finding was a bilateral Babinski reflex. There were no pupillary changes. The laboratory tests all gave normal or negative results. Eight days later the patient became comatose, fibrillary twitching developed, and he died.

Examination of the brain showed grossly that the markings of the cortex were obliterated in both frontal poles, owing to edema of both frontal lobes

CASE 5—A white man aged 31 was in a slightly disoriented state on admission. He had been in fairly good health, except for occasional periods of drinking, until two weeks prior to admission, when anorexia and generalized malaise developed and lasted about two days. Then he had a generalized convulsion, which was followed by severe headache, sleepiness and a temperature as high as 102 F. Examination revealed that the patient was lethargic and acutely ill, with a temperature of 99.8 F, a pulse rate of 88, a respiration rate of 20 and a blood pressure of 124 systolic and 85 diastolic. The right pupil was slightly larger than the left, and the visual fields demonstrated bitemporal constriction. The Oppenheim and Kernig signs were elicited. The blood count and hemoglobin were normal. The spinal fluid was clear and under a pressure of 300 mm, and the cell count was 400 lymphocytes per cubic millimeter. The patient rapidly became worse and died on the third day after admission.

Examination of the brain showed grossly that the convolutions were slightly flattened and that there was a small amount of terminal subarachnoid hemorrhage of focal distribution, chiefly dorsolateral and frontal. There was also softening of the anterior third of the left temporal lobe. Sections of the hypothalamus showed continuation of this softening back to the insula and the lenticular nucleus. There was also hemorrhagic extravasation into the tegmental portions of the midbrain and fusiform hippocampal gyri of the same side.

The superficial changes in the brains in these cases were not consistent. However, within the brain stem of all 5 brains there was periaqueductal hemorrhage, which was apparent grossly in 2 of them. The cause of death in all 5 cases was polioencephalitis hemorrhagica superior.

#### BIOCHEMICAL FACTORS

The pathologic condition known as polioencephalitis hemorrhagica superior has been found associated with scurvy in nonalcoholic patients, as well as in alcoholic patients (Alexander and others<sup>4</sup>). In view of the fact that the ascorbic acid level in the blood plasma of patients with psychoses due to chronic alcoholism is consistently low, one might be led to the assumption that this disease is a cerebral form of scurvy. However, further experimental work by the previously mentioned investigators demonstrated that in pigeons the disease could be produced by thiamine deficiency, particularly if the birds were fed a sufficient supply of one or more other vitamins, namely, vitamin A, riboflavin, ascorbic acid and vitamin D, and that this disease could not be produced experimentally by a deficiency in ascorbic acid. However, deficiency in ascorbic acid may play a role in the predisposition to the disease. The conclusions reached by Alexander and associates<sup>4</sup> were as follows. The clinical symptoms of thiamine deficiency in the pigeon are specific

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4 Alexander, L., Pijoan, M., Schube, P. G., and Moore, M. Cevitamic Acid Content in Blood Plasma in Alcoholic Psychoses, *Arch Neurol & Psychiat* 40:58 (July) 1938.

101 beriberi, e g, ataxia, convulsions and local paresis, the total solids of the brain are decreased and the water content is correspondingly increased, the mineral skeleton of the nerve tissue, in contrast to similar conditions of other causes, remains unaltered and may be responsible for the reversibility of the process, the lesions of polioencephalitis hemorrhagica superior can be produced in pigeons lacking thiamine, especially if they receive other vitamin complexes, such as vitamin A, riboflavin, ascorbic acid and vitamin D, polioencephalitis hemorrhagica superior cannot be produced by deficiency of ascorbic acid and the administration of vitamin A, riboflavin and vitamin D in cases of thiamine deficiency delays the onset of beriberi and prolongs the course of the disease once it is established

Beriberi is characterized clinically by degenerative changes in the nervous system, including polyneuritis, which may exist alone but which is often accompanied by generalized edema and serous effusions and by a tendency to the development of cardiac hypertrophy, which frequently results in cardiac failure and sudden death

#### HISTOPATHOLOGIC STUDY

The 5 brains which were studied in this investigation were fixed in solution of formaldehyde U S P (1:4). The brain stem in each case was separated from the cerebral hemispheres, and transverse sections were cut through the midbrain, pons and medulla. Transverse sections from each of these brain stems were treated with the following staining procedures: hematoxylin and eosin, for the general histologic changes, the Cajal reduced silver method, for changes in neurons and neurofibrils, the Cajal gold chloride-mercury bichloride ("gold-sublimate") method, for changes in the astrocytes, and the Penfield combined method, for changes in the oligodendroglia and microglia.

*General Histopathologic Changes* — Examination of microscopic sections of the brain stems stained with hematoxylin and eosin showed that the histopathologic changes in all 5 cases were confined largely, but not entirely, to the periventricular gray matter of the midbrain and the pons, i e, throughout the hypothalamus, the mammillary bodies, the medial parts of the thalamus on each side, the inferior colliculi and, to some extent, the floor of the fourth ventricle. Throughout the midbrain and below the aqueduct of Sylvius in the pons were areas where the parenchyma was more or less loosely arranged and was undergoing subacute necrosis and where the capillary blood vessels appeared to be increased in size and in number.

The walls of the capillaries showed proliferation of their endothelial cells and of the cells in the surrounding elastic and fibrous layers. The changes in the walls of the capillaries appeared to be due to this proliferation (fig 1 A and B). The perivascular spaces were enlarged in general in the areas affected.

In the localities of these parenchymal and vascular changes there were areas of old and fresh hemorrhage, which might be either extensive or rather small and which were perivascular. Old hemorrhage was usually indicated by the presence of pigment in the cells within the vicinity of the hemorrhage and in the perivascular spaces. The destruc-

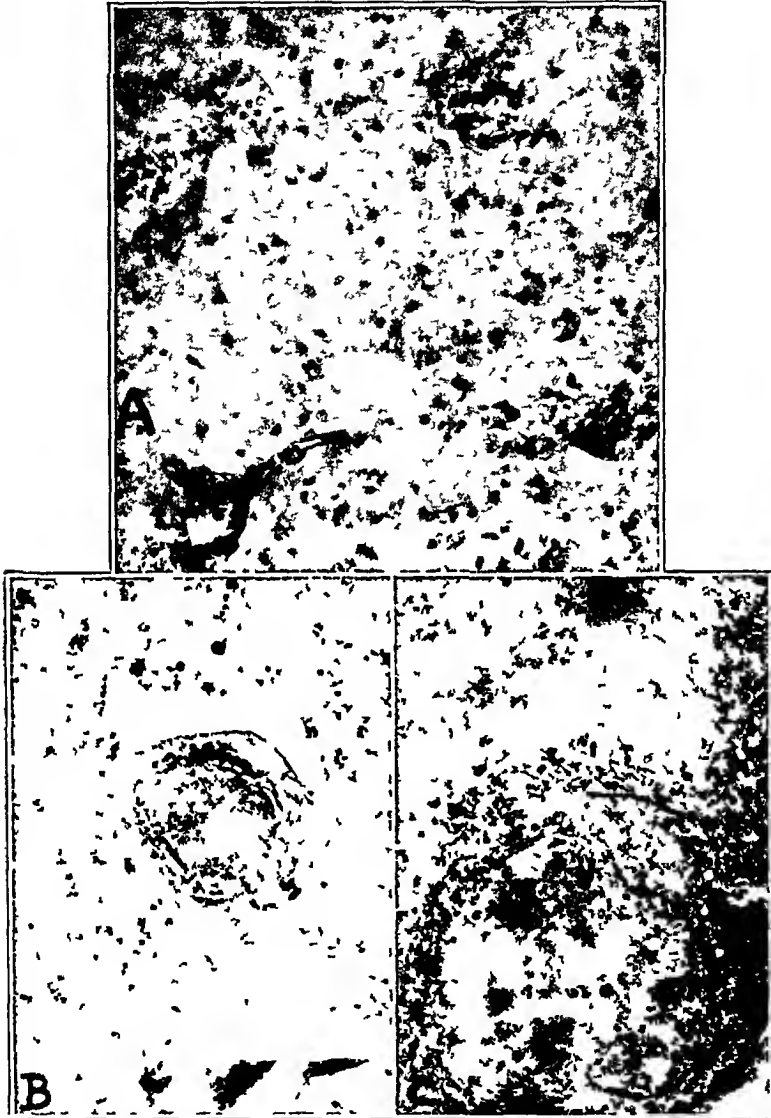


Fig 1—*A*, proliferation of the endothelial cells of the capillaries, *B*, loosely arranged capillary endothelium and pigmentary infiltration of nerve cells, *C*, extravasation of blood between endothelial cells of capillary  $\times 315$

tion of tissue might be so great as to obliterate the capillaries. In the areas of fresh hemorrhage the endothelial cells of the capillary vessels were loosely arranged (fig 1 *B*). The blood cells of the exudates were scattered between the endothelial cells through the perivascular spaces.

and into the surrounding tissue (fig 1 C) These hemorrhages were sometimes limited to the area about a capillary or sometimes so extensive as to cover an area approximately 1 to 10 mm in diameter

Focal areas of necrosis in the parenchyma varying in size from 1 mm to several millimeters in diameter were also observed Other areas were small and punctate, being only a fraction of a millimeter in diameter and scattered throughout a given area There was no evidence of leukocytic infiltration except in case 3, as described hereafter

Sections through the cortex showed no definite alterations in the cell arrangement or structure in any of the 5 cases studied and revealed changes in the leptomeninges in only 1 case In the first case, the perivascular and pericellular spaces were enlarged The leptomeninges showed chronic thickening and fibrosis There was a marked degree of softening in the tissue beneath the pia mater, an increase in the endothelial cells of blood vessels in this region and extravasation of blood

Special mention should be made of changes which were not characteristic of all the cases studied In the second case small focal hemorrhages occurred in the medial nuclei of the thalamus in addition to the changes previously described A section from the pons in the third case showed considerable leukocytic infiltration into the subarachnoid spaces and into the perivascular spaces A very large area of hemorrhagic necrosis involved almost half of one side of the section In the fifth case there were a number of small areas of hemorrhagic softening on one side in the pontile region

*Histopathologic Changes in Neurons and Axons*—Examination of microscopic sections of the midbrain and pons stained by the Cajal reduced silver method showed in all 5 cases focal neuronal degeneration within areas, or within the neighborhood of areas, of hemorrhage and necrosis

Within the sections from these regions of the brain stem were to be seen nerve cells far removed from the areas of hemorrhage and necrosis in which there was infiltration of dark brown pigment throughout the cytoplasm of the cells The pigment was of hematogenous character, originating from the disintegration of blood cells It had probably been carried into the nerve cells in finely divided state during the process of absorption and was then condensed into granules within the cytoplasm (fig 2 A) These cells had not undergone any apparent degeneration

At the periphery of other areas of hemorrhage and necrosis nerve cells had undergone acute swelling or chromatolysis some of which were in the more advanced stage of acute degeneration Some of these cells also showed pigmentary infiltration (fig 2 B) Where acute disintegration had taken place, the axons and dendrites had disintegrated

to a greater or less degree, and only fragments or granules of argento-philic material were visible (fig 3C)

Characteristic changes in the neurofibrillar apparatus, such as coarse and fine granulation, could also be discerned. These changes occurred in neurons at the margins of and within areas in which necrosis was

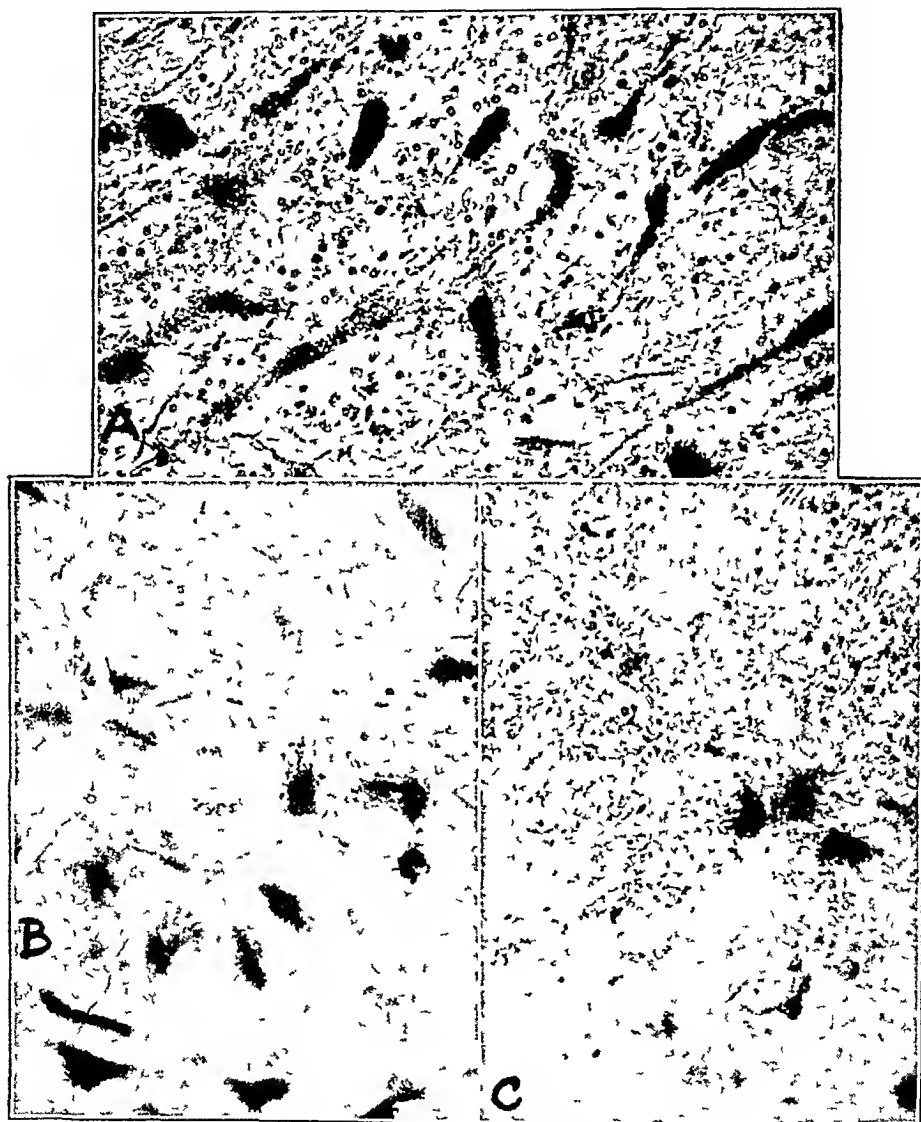


Fig 2—A, pigmentary infiltration, B, acute degeneration, and C, advanced degeneration, of nerve cells  $\times 358$

beginning or was under way. The cell in the early stage of change was not swollen, and its cytoplasm was filled with round, coarse, darkly stained granules. In later stages the cell might be slightly swollen, the cytoplasm was characterized by loss of detail and the nucleus might be slightly triangular. The cytoplasm of these cells contained fine

round granules in various groupings. In some cells the granules were collected in the center and the periphery was a clear zone (the hirudiform alteration of Cajal). In other cells there were fine granulations, with less seriously damaged fibrils along one border of the cell. Other cells

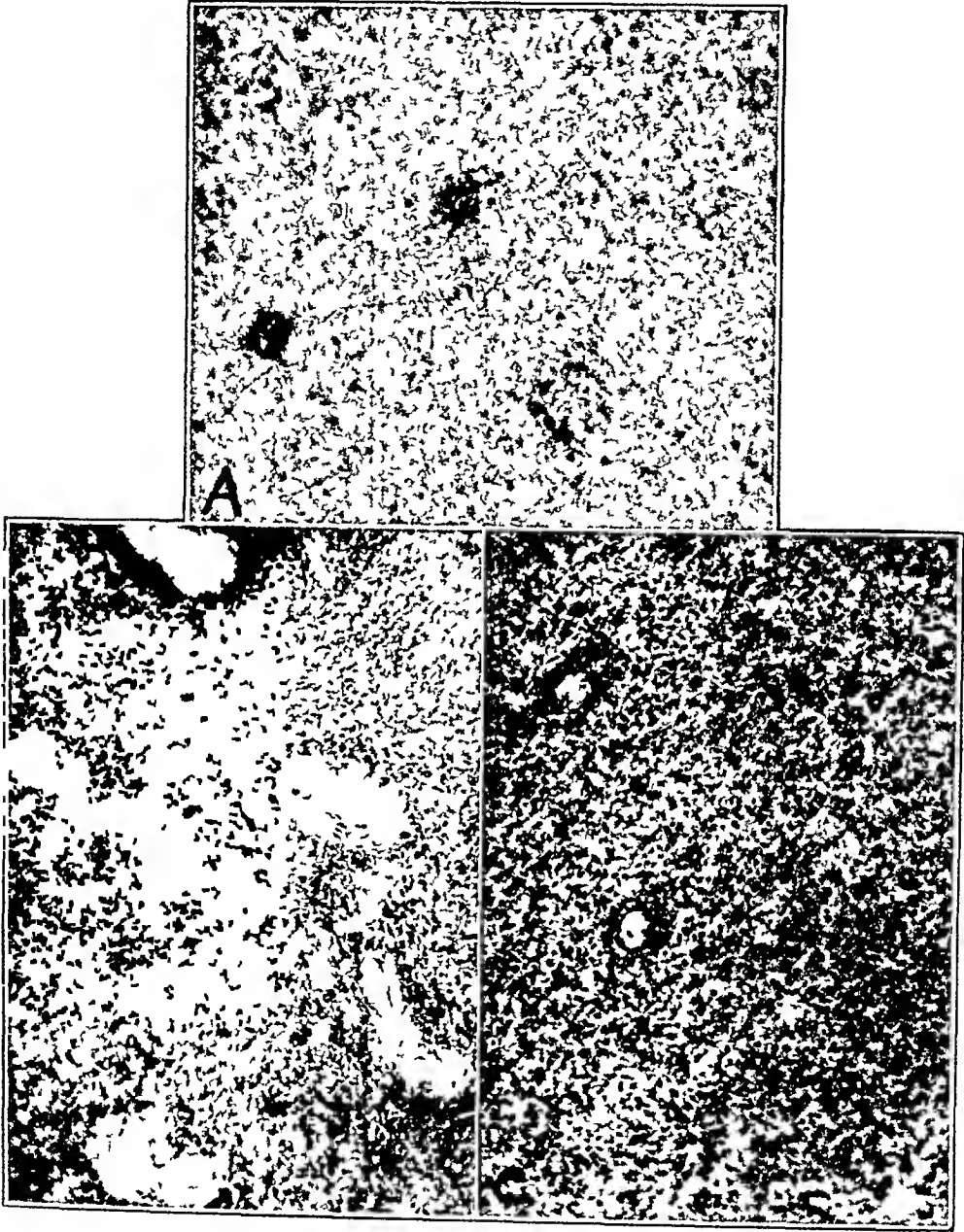


Fig 3—*A*, punctate necroses ( $\times 300$ ), *B*, fusion of necrotized spaces ( $\times 300$ ), *C*, complete destruction of neuronal elements ( $\times 74$ )

showed coarse and fusiform degeneration of neurofibrils (fig. 2 *C*). The extreme change in these cells consisted of an almost clear cytoplasm, containing a nucleus in the last stage of disintegration and very fine, darkly stained granules, which were irregularly and unevenly distributed. This series of changes in the nerve cells is known as hyalinization.



In addition to the hemorrhagic areas and areas of widespread necrosis, there were areas of punctate necrosis at various levels of the midbrain and pons. Many of these punctate areas were far removed from any hemorrhage and appeared in tissue in which the neighboring nerve cells had not undergone any degenerative changes. Each of these punctate spots of necrosis was surrounded with a ring of nerve fibers in which the silver stain had become much reduced. In some of these spots the center was deeply stained as well, in others the center contained shreds or strands of nerve fibers which were stained less deeply and formed a fenestra with a lattice-like arrangement of fibers (fig 3 A). These punctate spots of necrosis were observed also in the hematoxylin-eosin preparations.

In some other areas of multiple punctate necrosis the necrotized spaces had retained their dark brown borders. In other areas the borders of these spaces had more or less broken down, so that they communicated with each other. Fine strands of nerve fibers, which had been spared from destruction, formed a delicate lattice work within these enclosures. There was also widespread acute disintegration of nerve cells in the surrounding areas (fig 3 B).

In areas where complete destruction of all neuronal elements had occurred as a result of necrosis there was scattered a fine, darkly stained material, irregular in size and shape (fig 3 C). Many of these areas were far removed from any site of hemorrhage and might or might not have punctate areas of necrosis within or near them.

Acute swelling and hyalinization of nerve cells are indicative of interference with the chemical processes in the tissue because of undernourishment and lack of oxygen supply. The mechanism underlying this process may be based either on an ischemia or a toxemia.

*Histopathologic Changes in Neuroglia*—It was of particular interest to determine the nature of the reaction of the neuroglia in this study, as to my knowledge the reaction of the three neuroglial elements to the changes which take place in poliоencephalitis hemorrhagica superior have not been reported fully. The reactions of the neuroglia to laceration and to mechanical injury have been studied extensively, both in animals and human beings.<sup>5</sup> There are other destructive processes, however, which take place in brain tissue resulting in regressive changes, which may be chronic or acute. The changes which had taken place in the tissues of these brains were evidently acute, resulting in focal necrosis, and were apparently the culmination of long-standing or chronic metabolic disturbances.

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<sup>5</sup> del Rio-Hortega, P, in Penfield, W. Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932, vol. 2. Rand, C. W., and Courville, C. G. Histologic Studies of the Brain in Cases of Fatal Injury to the Head, Arch. Neurol. & Psychiat. **27** 1342 (June) 1932.

**Astrocytes** The changes in the astrocytes were proliferative, degenerative and, to some degree, transformative. Proliferation of these neuroglial cells was prominent in certain areas, not necessarily around an area where tissue destruction was acute (fig 4 *A*). It is

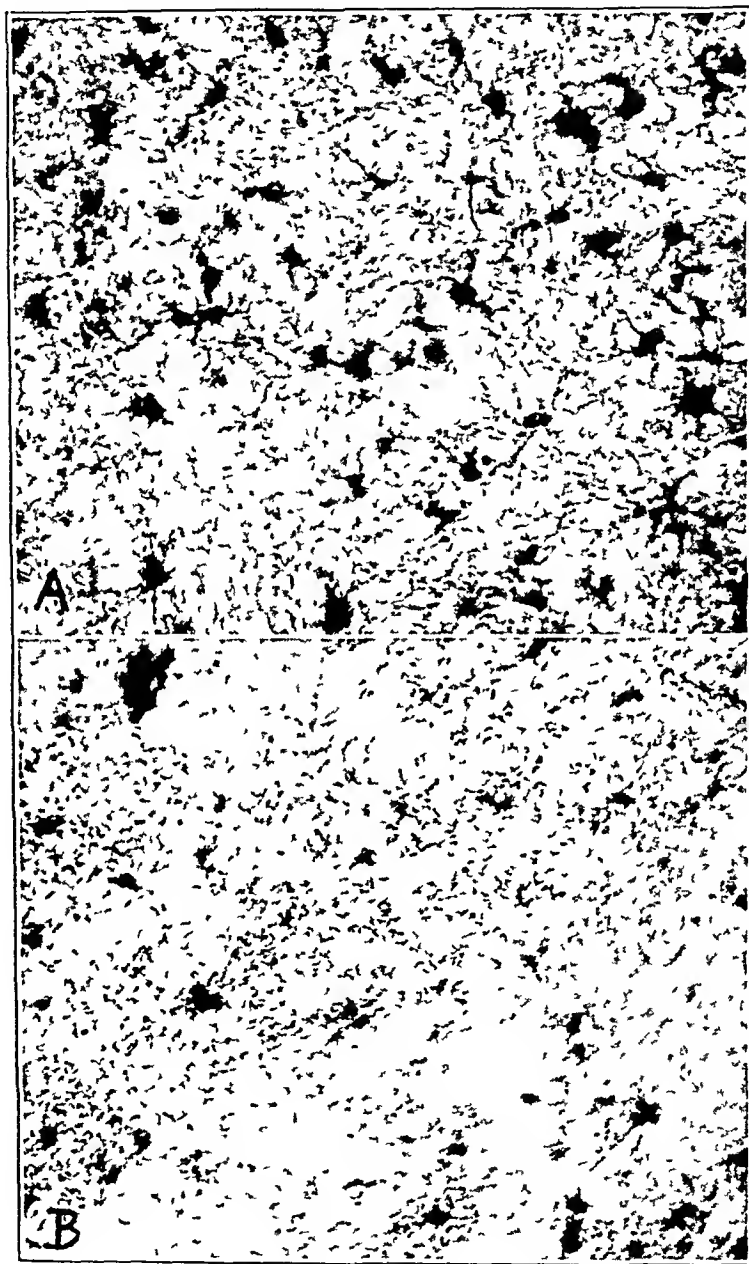


Fig 4—*A*, localized gliosis in area of necrosis, *B*, astrocytes undergoing degenerative changes  $\times 292$

indicative of stimulation by an irritative substance or by deprivation of blood supply<sup>6</sup>. The type of degeneration was that of acute destruction

<sup>6</sup> (a) Platt, B. S., and Lu, G. D. Chemical and Clinical Findings in Beriberi with Special Reference to Vitamin B<sub>1</sub> Deficiency, *Quart J Med* 5: 353, 1936.  
 (b) Riggs, H. E., and Boles, R. S. Wernicke's Disease, *Quart J Stud on Alcohol* 5: 361, 1944.

The astrocytes in the midst of this acute destructive process were undergoing immediate and complete necrosis and clasmotodendrosis. At the periphery of such an area some of the astrocytes could be seen undergoing transformation (fig 5 *A* and *B*). Many fibrous astrocytes were observed here, but occasionally astrocytes of the protoplasmic type could be seen forming neuroglial fibrillae. Transformation has been observed in degenerated areas following asphyxia.

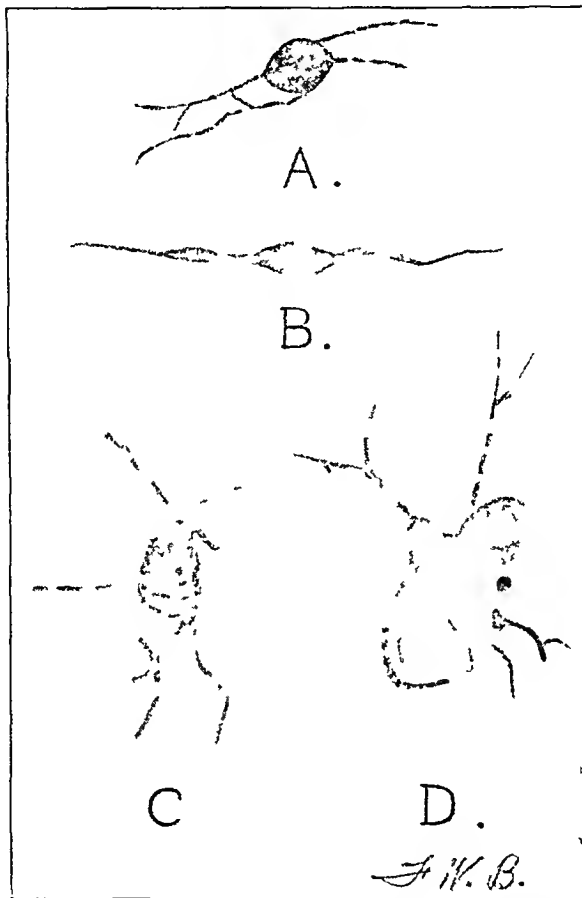


Fig 5—Pathologic changes observed in astrocytes. *A*, changes leading to formation of a pilonidal astrocyte, *B* and *C*, clasmotodendrosis of astrocyte, *D*, hyalinized, swollen astrocyte, or *gemastete Zelle*.

The astrocytes undergoing degenerative change were to be seen in the midst of the area of acute destruction which had undergone complete necrosis. The cell bodies not only had lost their processes but were fragmented and disintegrated. Astrocytes which had been killed but not destroyed had undergone a slower process of disintegration, namely, clasmotodendrosis (fig 5 *C*). The cells had lost their processes

7 Courville, C. B. Asphyxia as a Consequence of Nitrous Oxide Anesthesia, *Medicine* **15** 129, 1936.

by fragmentation, and the fragments had become granules. In some cells the cytoplasm contained granules, in others there were vacuoles, and in others there were both. No nuclei could be identified. The loss of the cell processes and the changes in the cytoplasm gave the cell an ameboid appearance, and this form has been termed the swollen

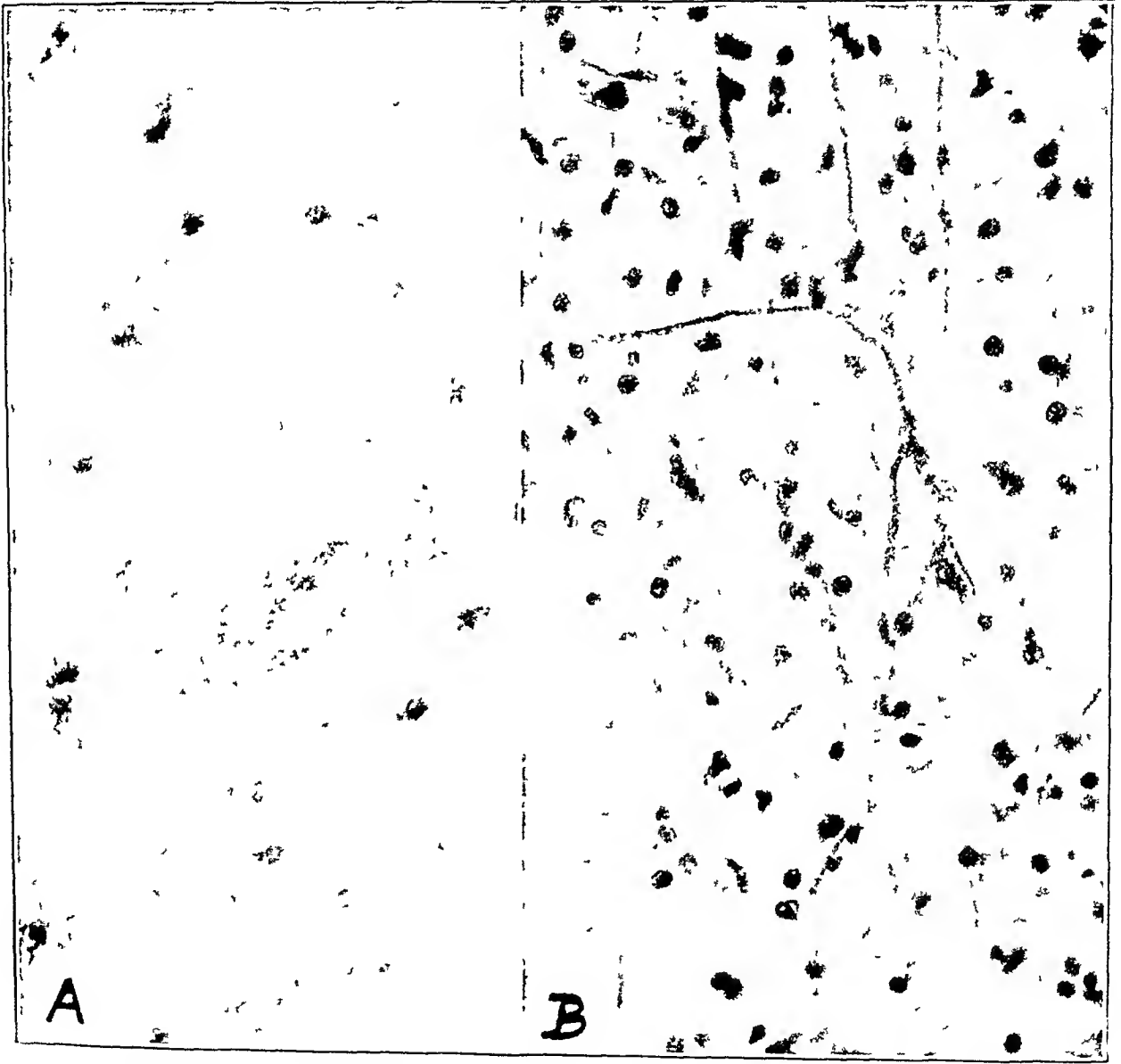


Fig 6—A, normal astrocytes and sucker feet, B, perivascular oligodendroglia  $\times 385$

astrocyte, or *gemastete Zelle*. It resembles the ameboid stage of the microglia cell (figs 4 B and 5 D). The latter, however, has a definite nuclear structure within it.

The degenerative changes of the astrocytes were indicative of the rapidity and nature of the destructive processes. Cells which had undergone complete necrosis were indicative of areas of acute destruction.

whereas cells which were undergoing clasmatodendrosis were indicative of areas of slower destruction

In other areas of these sections of the brain stem where the tissue was more normal, protoplasmic astrocytes could be seen. Some of these cells possessed long processes, the sucker feet, which extended to and were attached to blood vessels (fig 6A)

**Oligodendroglia** The changes in the oligodendroglia in response to the pathologic processes in this condition were chiefly those of acute swelling and of oligodendrogliosis (multiplication of cells) to a slight degree. These changes could be seen in areas undergoing partial or complete necrosis.

The phenomenon of acute swelling was characterized by marked enlargement of the cell, due to an accumulation of fluid within its cytoplasm in the form of vacuoles, the loss of cell processes, and nuclear pyknosis, the nucleus becoming central or eccentric in position. Acute swelling of the oligodendroglia cells was quite prevalent throughout the necrotic areas in the first and second cases, with coma of fourteen weeks and twelve days respectively before death, and, to a lesser extent, in the tissues in the other cases. Cell bodies undergoing hypertrophy, with increase of protoplasm and loss of cell processes preliminary to swelling, could be identified in both mildly necrotic and completely necrotic areas. Areas of moderate and complete necrosis contained cell bodies undergoing progressive hydropic swelling. The cell membrane appeared distended with clear fluid, through which extended strands of cytoplasm, while cytoplasmic granules were observed at the periphery. In some cells only granular fragments indicated where the strands were (fig 7). The nuclear material in a large number of the cells was divided to form two, three and four masses. The processes extending from the cells were fragmented and in some instances had disappeared. Acute swelling has been observed before in pathologic conditions which have a toxic influence on the brain and appears to be an invariable accompaniment.<sup>8</sup>

In the first case there were tissues which contained areas undergoing partial necrosis in which perivascular oligodendrogliosis could be identified, appearing as concentrations of cells grouped about blood vessels (fig 6B). This phenomenon did not occur in all areas of partial or complete necrosis. It is of interest to note that the first patient had been in a semicomatose state for three and a half months prior to her death. In the other cases studied the patients passed through periods of coma of much shorter duration. It is of significance that the phenomenon of perivascular oligodendrogliosis occurred only in this case of long-standing toxic state. It has been observed before in a

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8 (a) von Meduna, L. Beitrage zur Histopathologie der Mikroglia, Arch f Psychiat **82** 123, 1927. (b) Penfield, W. Cytology and Cellular Pathology of the Nervous System, New York, Paul B Hoeber, Inc, 1932, vol 2, p 465.

variety of conditions, particularly in toxic encephalitis of childhood, and is thought to be the result of long-continued edema or toxic state

**Microglia** The microglial cells appear to be scattered at random in the nerve tissue, but there are other cells which are located near nerve cells (neuronal satellites), blood vessels (vascular satellites) and astrocytes (neuroglial satellites) The first two structures were identified in the tissues studied The third was not identified The microglial cells actively intervene in all inflammatory and necrotizing

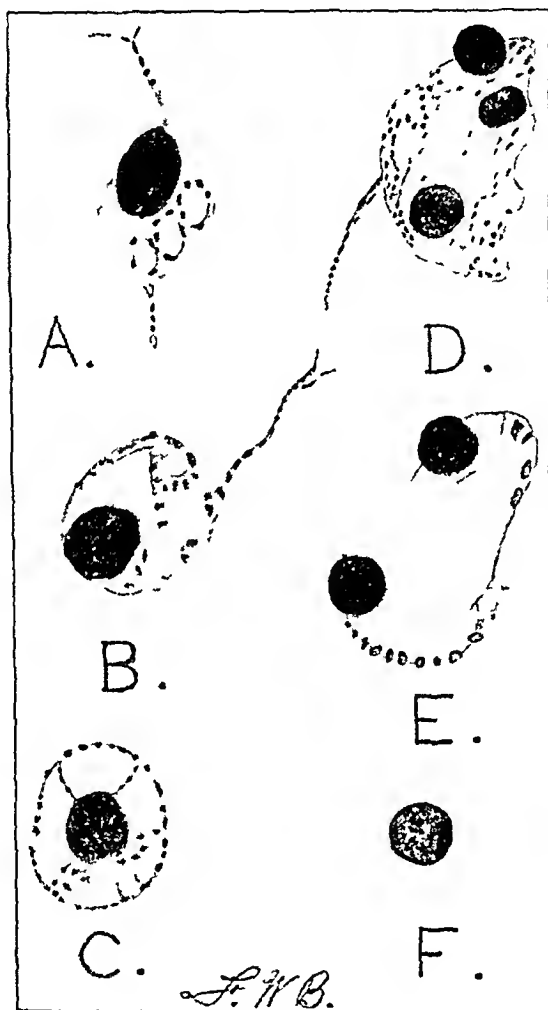


Fig 7—Acute swelling of oligodendroglia, showing the various stages from earliest swelling to destruction of the cell A, early stage of hypertrophy, B and C, stages in swelling of the cell, D, cell division, E, destruction of cell, F, nucleus left after destruction of cell

processes in nerve tissue As a result of their motility and function as macrophages, they undergo three types of change acute swelling, formation of rod cells and formation of compound granular corpuscles

Examination of the tissues stained with the Penfield combined method showed normal microglial cells in the normal areas In the areas of rapid degeneration, as in the areas of focal necrosis, normal microglia cells

were observed at the edge of, and occasionally within, the necrotic focus. Evidently, the pathologic change that occurred in such areas took place so rapidly that the microglia in these areas had not had enough time to undergo change. The microglia cells, including the neuronal and vascular satellite cells within the areas of focal necrosis, passive congestion and fresh hemorrhage, showed no pathologic changes or reactions.

In areas of ischemia and early to advanced generalized necrosis, acute swelling of microglia and formation of rod cells to some extent were observed.

Acute swelling is the first visible change in the microglia cell in any destructive lesion of nerve tissue and consists in an increase in volume, affecting first the cell processes and then the body. The processes of the microglial cells observed became transformed into thicker processes, which lost their spines and tended to become knotty and to form vacuoles. A later stage was observed in which the dendrites were still shorter and thicker and the cell body more swollen. Microglial cells undergoing acute swelling were numerous in areas of ischemia and early necrosis (fig 8A).

There could be seen also the occasional microglial cell which was becoming elongated to form a rod cell. The processes at the sides of the cell body were undergoing retraction and disintegration, while the processes from the opposite poles were preserved. These rod cells were seen within or at the periphery of areas of ischemia and early necrosis.

Acute swelling of microglial cells and formation of rod cells have been stated by some investigators to be produced by endogenous intoxication or by acute infection<sup>8b</sup>. However, previous destruction of the nerve structures is required for these reactions on the part of the microglia, and such a condition has been observed in very acute intoxications. The acute swelling of the microglia cells in these cases of poliomyelitis hemorrhagica superior is another instance of their response to an acute intoxication, accompanied with destruction of nerve tissue. The toxins produced are of endogenous origin. In exogenous intoxications no changes in the microglia have been observed.<sup>9</sup>

In areas of advanced necrosis and hemorrhagic areas of some duration the formation of compound granular corpuscles and their phagocytic action could be observed (fig 8B). The transformation of microglial cells into compound granular corpuscles consists in a series of changes. First, there is an increase in the cytoplasm of the cell, followed by enlargement with shortening and swelling of the expansions. The cell body becomes vacuolated, some of its expansions drop off, and

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9 de Villaverde, J. M. Lesions du cervelet dans l'intoxication par le plomb, Trav. du lab. de recherches biol. de l'Univ. de Madrid 25 41, 1927. von Meduna<sup>8a</sup>

it assumes an ameboid appearance, with short blunt processes. The cell finally assumes a globular shape, after it has ingested debris formed as a result of tissue destruction, to form the compound granular corpuscle. These various stages were present in the hemorrhagic areas with necrosis and in the areas of advanced necrosis in the tissues which were studied.

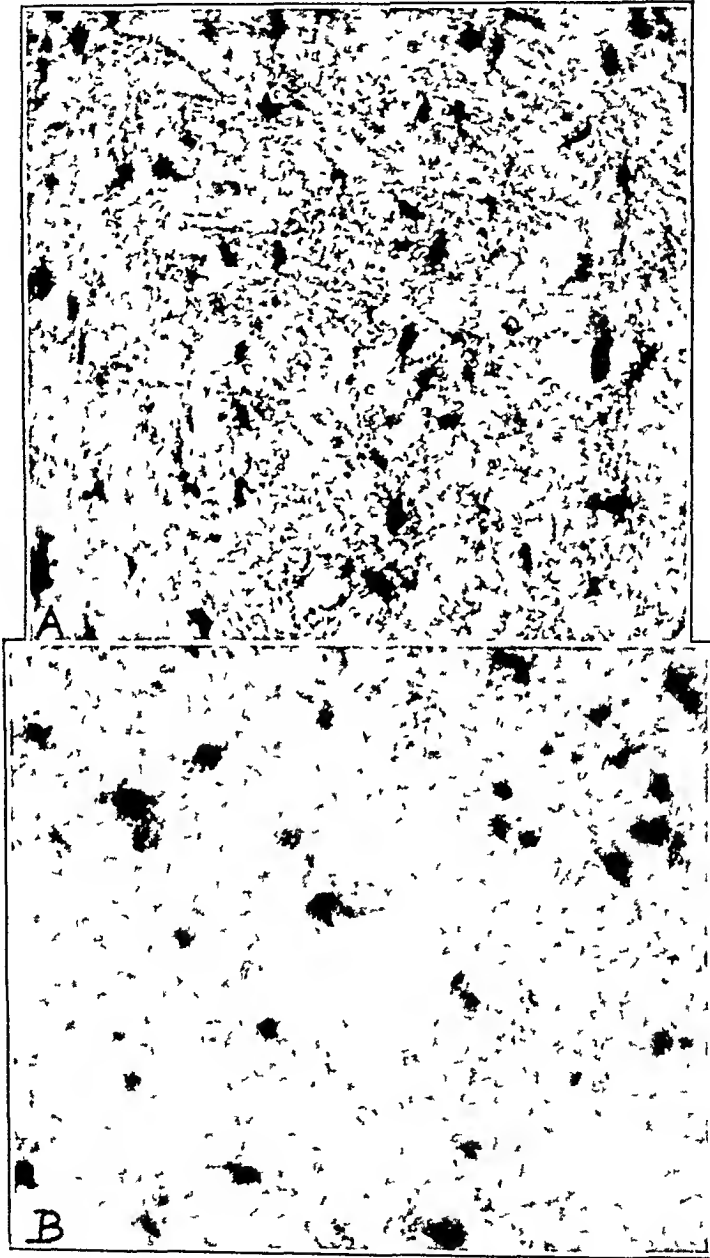


Fig 8—*A*, microglial cells undergoing acute swelling, *B*, compound granular corpuscles containing phagocytosed material  $\times 256$

(figs 8 *B* and 9) In areas where there was hemorrhage but no necrosis no microglial changes were evident. It was observed, however, that the microglial cells within or close to the area of destruction were the first to undergo transformation and become phagocytic.



Careful study of all the areas of destroyed tissue showed no actual migration of compound granular corpuscles into them. In these areas there was an increase in the number of the phagocytic cells, but it was apparently due to the transformation of the microglial cells already there, for it was obvious that no normal microglial cells were present (fig 8 *B*). Instead of the normal microglial cells, the various stages

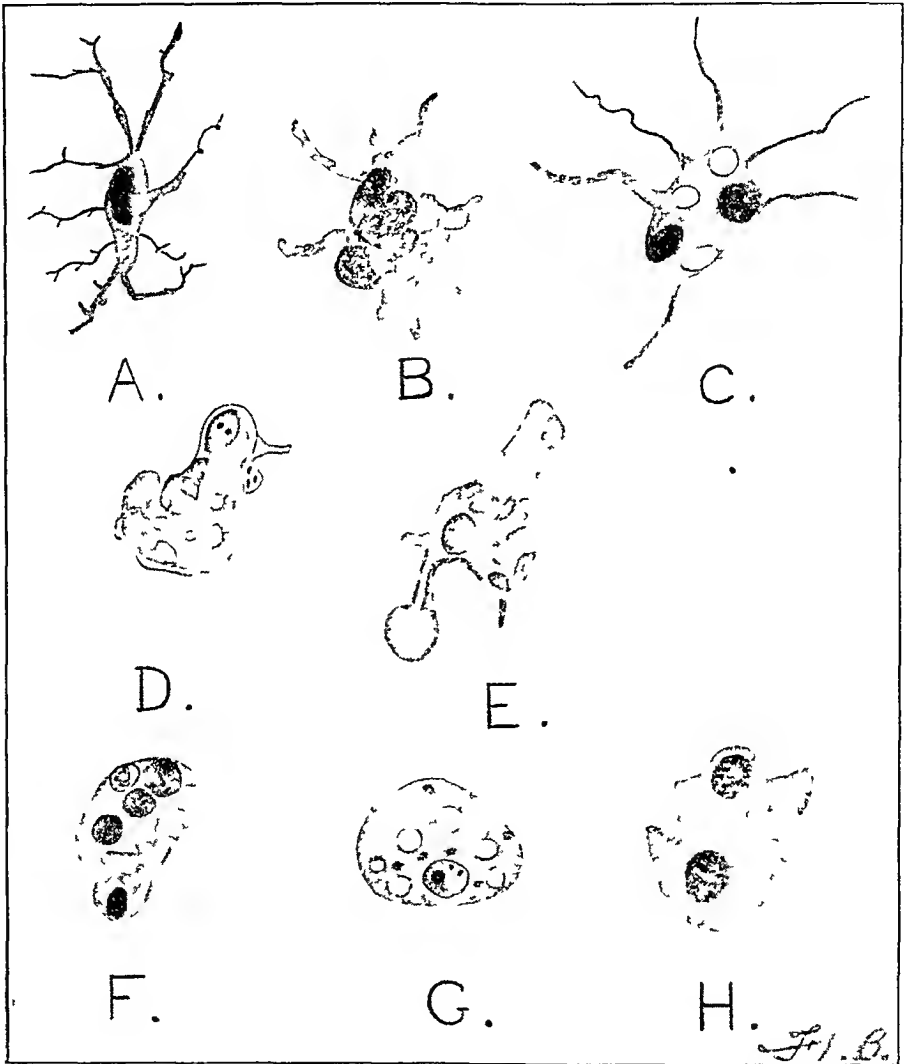


Fig 9—Changes in the microglia cell during its phagocytic activity *A*, cell with rough long processes, *B*, cell with enlarged cell body and smooth, short processes, *C*, hypertrophic cell with pseudopodia, *D*, ameboid form, *E*, ameboid form containing granules of ingested material, *F*, globular form containing phagocytosed erythrocytes, *G*, compound granular corpuscle, *H*, corpuscle dividing

of these cells could be seen, such as the acutely swollen cell with pseudopodia, the ameboid cell and the globose cell (the compound granular corpuscle) with ingested debris and blood cells. Mitotic

division of some of these cells could be observed occasionally, and increase in the number of these phagocytic cells in a given area was evidently also based on division of these cells

In the destroyed or degenerated areas of the brain studied the compound granular corpuscles could be seen in the process of phagocytosing red blood cells and the degenerated products of necrosis. In old hemorrhagic areas a very small number of these ameboid cells were observed to have erythrocytes within them. Such cells were located within areas where there were small capillary hemorrhages with capillary budding. In the areas of massive hemorrhage no phagocytosis was observed. It appears that the hemorrhage was of such a sudden and extensive nature that the microglia had not had time to assume the phagocytic function.

The macrophagic function of the microglia evidently takes place slowly, by its metamorphosis, to form compound granular corpuscles. This neuroglial element undergoes modification during intense inflammatory conditions, during local disintegration of nerve tissue and apparently where there is hemorrhage of the exudative type of some duration.

#### PATHOLOGIC MECHANISM OF PRODUCTION OF LESIONS

The reactions of the various cellular elements are indicative of responses to the stimuli from toxic substances, from focal necrosis and from local hemorrhage which are produced by chemical changes in the tissues.

In view of the fact that thiamine deficiency contributes to polioencephalitis hemorrhagica superior, even when other vitamins are fed, the chemical factors which underlie this condition are to be considered. Funk<sup>10</sup> suggested that thiamine has some role in the metabolic transformation of carbohydrate in the animal body. Further studies indicated that a high carbohydrate diet is much more effective in producing the symptoms of thiamine deficiency than one high in fat. Westenbrink<sup>11</sup> suggested that during carbohydrate and fat metabolism thiamine is used at the same rate but when carbohydrate alone is metabolized a toxic metabolite arises which in the absence of the vitamin is not removed and which induces Wernicke's syndrome.

Lactic acid is a normal intermediate metabolite, which, in turn, produces pyruvic acid in the metabolic breakdown of glucose. Pyruvic acid is broken down by oxidative processes. Investigations have shown

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10 Funk, C. Studien über Beriberi. II. Die Rolle der Vitamine beim Kohlenhydratstoffwechsel, *Ztschr. f. physiol. Chem.* 89: 378, 1914.

11 Westenbrink, H. G. K. Ueber den Einfluss der Menge und der Zusammensetzung der Nahrung auf die Folgen von Vitamin-B<sub>1</sub> Mangel, *Arch. néerl. de physiol.* 19: 94, 1934.

that associated with thiamine deficiency there is an accumulation of pyruvic acid in the blood which is proportional to the deficiency<sup>12</sup> It can be reduced to normal by feeding thiamine (Platt<sup>6a</sup> and Thompson<sup>13</sup>) On the basis of these results, it is contended that thiamine brings about the oxidation of pyruvic acid and facilitates the absorption of oxygen by the tissues The fasting level of pyruvate in the blood is invariably elevated in cases of thiamine deficiency, and after it is supplied the fasting level of blood pyruvate rapidly returns to normal There is clinical improvement also<sup>14</sup>

It is evident that in the state of chronic alcoholism, in which there are a deficiency of food intake and a disturbance of nutrition, thiamine deficiency occurs This deficiency causes a faulty carbohydrate metabolism, with decrease in the amount of oxygen supplied to the tissues The deficiency of oxygen and the accumulation of pyruvic acid produce anoxia and necrosis in the tissues As a result of anoxia, the walls of capillaries become hypotonic The endothelial cells proliferate, which is the result of an attempt at capillary budding The attempt is soon aborted, the cells grow irregularly, instead of in the form of capillaries, and the walls become weak and varicose The parenchyma of the brain tissue takes on a loose appearance, for the reason that the cells are unable to secure enough oxygen so that they can develop from carbohydrate sufficient energy to perform their various and specialized functions

The more advanced states of focal necrosis, hemorrhage into the perivascular spaces and rupture of capillaries, are a result of further and prolonged interference with the normal function of the cells in the tissues and capillaries The effect of the anoxia and the toxic metabolites, together with the inability of the cells to derive sufficient energy from carbohydrate metabolism, is to decompose and interfere with the production of the intercellular substance of tissues in general The result is that the endothelial layer and the collagenous fibers which ensheath the capillaries become weakened and allow extravasations of blood and areas of degeneration and focal necrosis to develop in the parenchyma

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12 Peters, R A The Biochemical Lesion in Vitamin B<sub>1</sub> Deficiency, *Lancet* **1** 1161, 1936

13 Thompson, R H S, and Johnson, R E Blood Pyruvate in Vitamin B<sub>1</sub> Deficiency, *Biochem J* **29** 694, 1935

14 Jolliffe, N, Wortis, H, and Fein, H D The Wernicke Syndrome, *Arch Neurol & Psychiat* **46** 569 (Oct) 1941 Wortis, H, Bueding, E, Stein, M H, and Jolliffe, N Pyruvic Acid Studies in the Wernicke Syndrome, *ibid* **47** 215 (Feb) 1942

## SUMMARY AND CONCLUSIONS

1 The histopathologic processes underlying polioencephalitis hemorrhagica superior (Wernicke syndrome) are confined to the periventricular gray matter of the midbrain and pons, as well as the thalamus and the hypothalamus

2 These processes consist of focal areas of small capillary hemorrhages and of necrosis. Vascular disturbances include dilatation of the capillaries, capillary budding and perivascular hemorrhages. There is parenchymatous degeneration, consisting of loosening of the ground substance

3 Areas of widespread necrosis, of focal necrosis and of punctate necrosis occur. Within and near these areas there is neuronal degeneration, exhibiting acute swelling and hyalinization, changes indicative of interference with the chemical processes of the tissue due to lack of oxygen or inadequate elimination of toxic metabolites

4 The astrocytes show proliferation, transformation and degeneration. Proliferative and transformative changes are indicative of widespread stimulation of the astrocytes by an irritative substance or by deprivation of oxygen supply. The degenerative changes of the astrocytes are indicative of the rapidity and nature of the destructive processes

5 The changes in the oligodendroglia, which occur in areas undergoing partial or complete necrosis, are chiefly those of acute swelling and oligodendrogliosis. Acute swelling of oligodendroglial cells has been observed previously in pathologic conditions which exert a toxic influence on the brain and appears to be an invariable accompaniment of such states. The occasional occurrence of perivascular oligodendrogliosis in the tissues of the brain stem of patients who were in a semicomatose condition for long periods is indicative of a state of long-continued edema and toxemia

6 In areas of ischemia and in areas of early to advanced necrosis, acute swelling of microglia and formation of rod cells to some extent are observed. Previous destruction of the nerve structures is required for this reaction on the part of the microglia, and such a condition is observed in polioencephalitis hemorrhagica superior, which arises from a condition of acute intoxication. The toxins produced are of endogenous origin, although the causative agent, alcohol, is an exogenous one

In areas of advanced necrosis and in hemorrhagic areas of some duration the formation of compound granular corpuscles and their phagocytic action can be observed. In such areas there is an increase in the number of these phagocytic cells, but this is apparently due to the transformation of the microglial cells already there. There is no

evidence of migration of these phagocytic cells into the areas of destroyed tissue

7 Underlying the histopathologic processes there is a deficiency of nutritional factors, the chief of which is thiamine. A number of investigators of this syndrome have demonstrated that there is interference with carbohydrate metabolism and with oxidation of pyruvic acid and that there is a decrease in the amount of oxygen supplied to the tissues. The effect of the anoxia and the toxic metabolites is to interfere with the chemistry of the cells and to cause their degeneration, which results in necrosis of various degrees in the tissues of the brain stem and in weakening of the walls of the capillaries, with extravasation of blood.

Presbyterian Hospital

# CAPILLARIES IN THE FINGER NAIL FOLD IN PATIENTS WITH NEUROSIS, EPILEPSY AND MIGRAINE

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BOSTON

MICROSCOPIC studies of the capillaries of the skin in living persons go back to 1922, when Otfried Muller, in Germany, published his book<sup>1</sup> His studies did not concern the subject in which I have been interested He investigated the morphologic changes and the blood flow in capillaries of the skin in physical disease, such as disturbances of the heart and kidneys However, he and one of his co-workers, Parrisius,<sup>2</sup> have already described structural and functional abnormalities in so-called "vasoneurotic" patients

The term "vasoneurotic" is somewhat vague, so no clearcut relation of the findings of these authors to the now better established types of the neuroses can be given Some of their observations, especially on the structural abnormalities, agree with mine, others should be related, rather, to one group of neurotic patients only However, a great many of their observations on the abnormalities of the blood flow are, according to my studies, not characteristic of patients with vasoneurotic disorders, since one can find them also in normal persons

It is difficult to determine the subjects who can be used as normal controls for observations on neurotic persons because normal persons may have one or another trait found also in neurotic patients I examined the capillaries of 125 so-called normal persons The group consisted of students of Tufts College Medical School, of nurses of the Pratt Diagnostic Hospital, of some physicians and of patients who had been in the hospital for reasons other than neurotic or neurologic troubles Of course, a number of those subjects, especially the students, were neurotic I did not know this prior to my examinations I exam-

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This research was supported by a grant from the Harrington Fund

From the Joseph H Pratt Diagnostic Hospital and the Boston Dispensary

1 Muller, O Die Kapillaren der menschlichen Korperoberfläche in gesunden und kranken Tagen, Stuttgart, Ferdinand Enke, 1922

2 Parrisius, W Kapillarstudien bei Vasoneurosen, Deutsche Ztschr f Nerven 72 310, 1921 Muller, O, and Parrisius, W Die Blutdruckkrankheit Klinische, erbbiologische, anthropometrische, biochemische, histologische, kapillarmikroskopische und andere Untersuchungen am Blutumlauf bei Hypertonikern, Stuttgart, Ferdinand Enke, 1932

ined the capillaries before I had interviewed the subject for the presence of neurotic traits. Ninety-three per cent of these normal persons had normal capillaries, 7 per cent showed the anomalies seen in neurotic patients. Therefore one can state with certainty that there exists a normal capillary picture in adult normal persons. I emphasize the word "adult," because children show a different capillary picture. There is a fairly regular change with age, although the development of the capillary picture from that of the newborn to the final pattern of the grown-up differs with different persons. It depends not only on the anlage of the ectoderm but probably also on environmental factors.

Studies on the development of the capillaries in children were the starting point of my investigations, which go back a number of years. It was Jaensch<sup>3</sup> who first inaugurated these studies and, together with two other authors, Hoepfner and Wittneben, published a book on his observations in 1929. In America, Powdermaker<sup>4</sup> published the results of corresponding examinations in the same year, and Leader<sup>5</sup> reported her observations in 1932. All these studies show that there is a rather strict relation between the development of the capillary picture and the mental development. For instance, examinations by German investigators showed that the capillaries of 67 per cent of children in a normal school displayed a normal pattern, whereas only 29 per cent of children of an ungraded school showed normal capillaries. Powdermaker obtained corresponding figures, and, what is more interesting, she did not find abnormal capillaries in those retarded children whose defectiveness was due to such factors as trauma, encephalitis and meningitis. She concluded that an examination of the capillaries may help to establish a diagnosis when the early history is inadequate to distinguish between a constitutional etiologic and an environmental factor. Similar were the findings of Leader, who observed normal capillaries in children with delayed physical development but with normal or superior intelligence. Another American author, Crawford,<sup>6</sup> went so far as to state that the capillaries are as characteristic in a given person as his face and that they remain essentially the same from day to day and from minute to minute.

This morphologic stability is true only in adults after the development of the capillaries has come to an end. As I mentioned before,

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3 Jaensch, W. *Die Hautkapillaroskopie*, Halle, Carl Marhold, 1929.

4 Powdermaker, F. *Capillary Forms in Relation to Certain Problems in Development*, *Arch Neurol & Psychiat* **22** 1207 (Dec.) 1929.

5 Leader, S. D. *Capillary Microscopy in Children*, *Am J Dis Child* **44** 403 (Aug.) 1932.

6 Crawford, J. H. *Human Capillaries. Observations in the Capillary Circulation in Normal Subjects*, *J Clin Investigation* **2** 351, 1926.

this end is different in different children. Powdermaker stated that the end stage may be reached as early as the age of 6 months or as late as 6 years. The German authors made the interesting observation that the development of the capillaries is delayed in children who grow up in a population in which goiter is endemic. Leader, in America, found that abnormal capillaries in myxedematous children developed rapidly in normal forms with thyroid medication.

The relation between retarded development of the capillaries and mental abnormalities in children is the only clue to the relation of the capillary pattern to the structure of the brain. The fact that the skin and the nervous system come from the same germinal layer does not mean much in this regard, especially as the capillaries originate in the mesoderm. Nevertheless, Jaensch expressed the belief that the evolution of the capillaries coincides with the myelination of the nerves and the differentiation of the cerebral cortex.

#### METHOD

I used an ordinary microscope with an eyepiece with a magnification of 75 and an objective lens with a magnification of 10. The best region for the observation of the capillaries is the finger nail fold. One can use other parts of the body, but the results are not so good, especially if one wants to make photographs. As the finger must be kept as steady as possible, I made a holder on the platform of the microscope with two walls, between which the finger could be kept in the proper place. By means of the two screws of the microscope table, the finger could be moved easily in all directions, which is necessary if one is to observe the capillaries in different parts of the finger. The skin just under the lens is covered with cedar oil in order to make it more transparent. One has to use a strong lateral light focused exactly on the spot of observation. I used a very strong electric bulb equipped with a special device at the side of the lens, so that it could be adjusted at different angles. This light, however, is not strong enough for making photographs. For photography I used an arc lamp with a green filter. This is necessary, otherwise one gets very poor pictures, such as are seen in most publications. One has to make very short exposures, as despite all fixation the patient is unable to keep the finger steady. The development of this technic is difficult and discouraging, but I found it necessary to spend much time on it, because drawings, such as have been used by most authors, are not convincing. Although I have succeeded in getting some good photographs, I must say that the microscopic observation is much more important. As the surface of the finger nail fold is curved, and not a plane, and as the capillaries are not all situated in the same layer, one has to focus up and down with the fine adjustment in order to see the whole structure of a capillary.

The visibility of the capillaries is dependent on the transparency of the skin. This differs with different persons, and even at different times. For instance, perspiration interferes with the visibility. Ordinary injuries of the fingers, with which I include manicuring, do not interfere with the visibility and the form of the capillaries. Environmental influences do not play any role. There are, however, a certain number of persons, approximately 10 per cent, with a skin too thick to permit good examination of the capillaries.



## NORMAL ANATOMIC PICTURE

The capillaries of the nail fold show a deep arterial network, a second, subpapillary network near the junction of the middle and the outer third of the cutis, and a third, even more superficial, arterial network beneath the papillae. From this network arise the capillaries in the papillae. Between these arterial layers are at least four venous plexuses. Only one capillary loop is present in each papilla.

The normal development of the capillaries may be summarized as follows (fig 1). At birth there are no capillary loops in the papillary layer. The upper part of the corium represents a flat line. There is a primitive network of vessels supplied by the arterioles and venules of

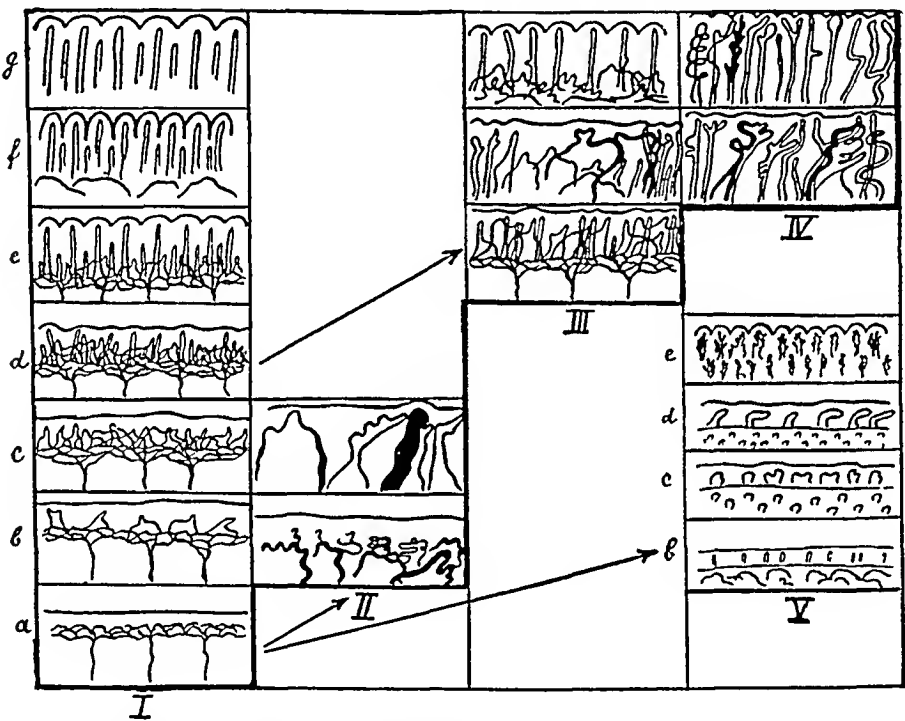


Fig 1—Development of capillaries in the newborn. The column at the left shows normal development (to be read from the bottom to the top). The other columns show arrested development in mentally retarded children. The arrows indicate the stage at which the development was arrested and went the wrong way.

the deeper layers. At the age of about 4 weeks saddle-shaped forms sprout from the primitive plexus. They grow gradually in the direction of the corium, but not before the fifth month does one find the hairpin-like capillary loops, each of which lies in a papilla. At the same time, the horizontal network of fine blood vessels decreases in size, and the corium becomes wavy. At the time when definite loops have developed, the corium assumes the scalloped appearance. At from the fifth or sixth month to one year of age the capillaries and the papillae develop into

the mature picture, as seen in *g* of figure 1. This figure, a drawing by Jaensch,<sup>3</sup> shows in the left column, which is to be read from the bottom to the top, the normal development of the capillaries in children. In the other columns, Jaensch has recorded the capillary patterns due to abnormal development in mentally retarded children. The arrows indicate at what stage the development has stopped. Column *V* shows a special hypoplastic, primitive stage, seen oftentimes in cretins. It is important to stress that at the end of normal development no horizontal network or subcapillary plexus can longer be seen.

The pattern of the normal capillaries in adults is as follows. The corium is well scalloped, and the papillae are rather regular. The capillaries of the first row are hairpin-like. The arterial limb is narrower than the venous limb. Figure 2 shows examples of normal capillaries. According to Muller, the width of the lumen is 0.009 to 0.012 mm.

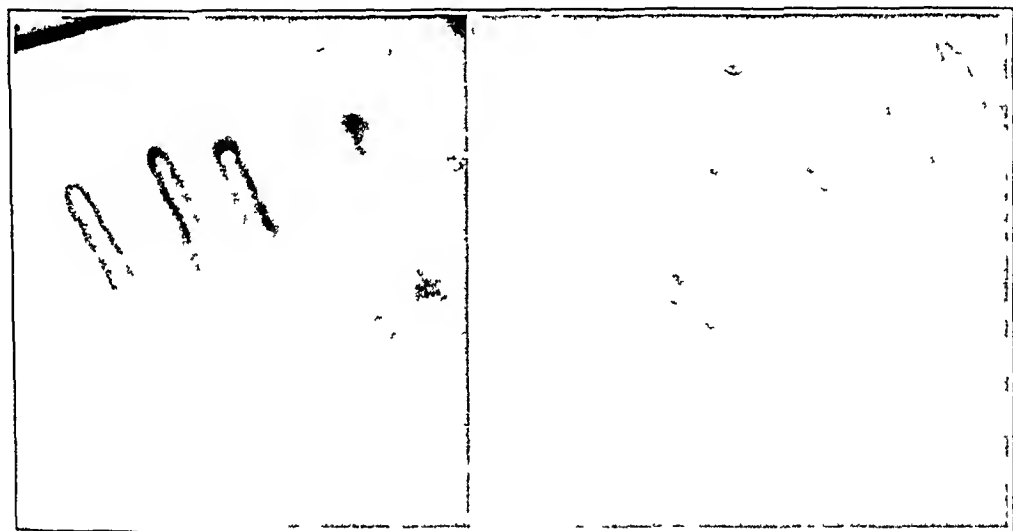


Fig 2—Normal capillaries in the adult. The photographs show the capillaries of the end row. They are hairpin-like, straight and evenly distributed.

My own figures are a bit higher—0.014 to 0.021 mm. These values correspond better than Muller's to the figures of Krogh,<sup>7</sup> who mentioned 0.02 mm as the width. According to Deutsch,<sup>8</sup> who made capillary studies in cases of Raynaud's disease, the height of the capillaries is 0.2 to 0.4 mm. My own figures are smaller—0.04 to 0.1 mm. I do not believe that these differences are important, as the size of the capillaries differs in different persons. I got the impression that there is some relation to the anthropologic bodily structure (leptosomatic, pyknic, athletic).

<sup>7</sup> Krogh, A. *Anatomy and Physiology of the Capillaries*, New Haven, Conn. Yale University Press, 1924.

<sup>8</sup> Deutsch, F. *Capillary Studies in Raynaud's Disease*, *J. Lab. & Clin. Med.* 26:1729, 1941.

It is important to stress that in normal adults no subpapillary plexus is visible. I emphasize this fact because the persistence, or, let me say more cautiously, the visibility, of a horizontal network of vessels in the proximal parts of the nail fold means, in my opinion, a pathologic pattern. Normally one does not see any connection between the capillaries in the first row and the deeper vessels.

The capillaries of the first row are not the only ones which are visible, although they are better visible, and their shape is more significant, than the capillaries of the proximal parts. Those capillaries are usually shorter, and they do not appear at the same angle as the capillaries of the first row. This may also be one reason for the shorter appearance, for one often looks vertically at the connecting part between the arterial and the venous limb.

The distribution of the capillaries is very even in normal subjects, especially in the first row. Irregularities in this regard are as significant as variations from the hairpin-like shape. Usually the capillary pattern is the same in all fingers and in both hands. I always studied the fourth and fifth fingers of each hand. The fourth finger is the best test object. On the little finger, even in normal persons, one is more likely to find variations in the distribution and form of the capillaries. Generally, in the little finger the abnormalities seen in the other fingers are magnified and multiplied. For instance, if there are a few abnormal structures in the fourth finger, one will find them more pronounced in the little finger. One never should examine one finger and one hand only.

Slight variations from the ideal pattern of the capillaries are not to be considered pathologic. If the variation concerned only a different shape of the capillaries in the end row, not the visibility of a horizontal network of vessels, I usually counted the number of abnormal capillaries in one visual field. This gave me the degree of abnormality, e. g., 5 or 10 per cent or more. The normal variations from the hairpin-like shape consist in some tortuosities or slight twisting or in figure 8 forms. If the abnormal forms exceed 20 per cent in a field, I do not consider the pattern normal. It belongs, then, in the category of the 7 per cent incidence of abnormal capillaries in normal persons, which I mentioned earlier.

#### OBSERVATIONS

*Neurosis*—I examined 578 abnormal subjects. This number consisted of 375 patients with neurosis, 117 with epilepsy, 37 with migraine, 21 with nonmigraine headache and 28 with other neurologic diseases.

I divided the 375 neurotic patients into 304 constitutionally neurotic persons and 71 with neurotic reactions. I called those patients constitutionally neurotic in whose family several other neurotic persons could be found and who obviously had inherited their neurotic anlage. Another

evidence of their abnormal constitution could be seen in the fact that neurotic traits appeared very early in life and could not be explained by environmental factors, such as unhappy home conditions or troubles in school or in their relation to friends. Neurotic traits persisted throughout their life independent of environmental circumstances, or even despite favorable conditions. The patients with neurotic reactions, on the contrary, were not nervous *ab origine*. In their families usually no other neurotic persons could be found. They did not show neurotic traits during childhood, even when the family life or their experiences during "teen age" contained noxious agents. It was not difficult to relate their neuroses to definite environmental circumstances, such as marital or family trouble, severe grief, difficulties in business or serious sickness. Oftentimes those reactive neurotic traits disappeared in the course of time and the patient remained normal until a new troublesome experience caused a second neurotic reaction. It goes without saying that there is no strict borderline between these two groups of neurotic patients, one may be in doubt occasionally whether a patient should be put in the one or in the other group. It was interesting that of the 304 constitutionally neurotic persons, 268, or 88.1 per cent, showed abnormal capillaries, whereas only 36, or 11.8 per cent, showed normal capillaries. Of the 71 patients with neurotic reactions, however, only 3, or 4.2 per cent, showed abnormal capillaries, whereas 68, or 95.7 per cent, had normal capillaries.

The shape of the abnormal capillaries in neurotic patients can be seen in figure 3. The papillae are not regularly built, they do not stay in one row, sometimes they are very shallow, and in cases of severe neuroses there are no papillae at all. Also, the distribution of the capillaries is irregular. They do not stay in clearcut rows, and they are not all oriented in the vertical direction. The most characteristic anomaly, however, is the tortuosity. They are twisted and sometimes show grotesque forms. The twisting is not restricted to one of the limbs. The caliber of the capillaries is often large. The most pronounced twistings appear in the capillaries of the end row, or at least they are best visible there. A certain percentage of neurotic patients showed a pattern which is also seen in mentally retarded children, and, as will be seen later, in epileptic patients. This pattern consisted of horizontal vessels in the proximal parts of the nail fold, sometimes even of a horizontal network of vessels. Oftentimes the capillaries could be followed into this network. This pattern can best be interpreted as a primitive stage, known from the development of the capillaries in early childhood. Of 586 persons (normal subjects and patients with neurosis, nonmigraine headache and other neurologic diseases) I found this pattern in 73, that is in 12.4 per cent. Interestingly, this immature picture was found especially in patients with

hysteria This corresponds with my conception of hysteria as a neurosis of primitive structure The most pronounced tortuosities could be found with anxiety neurosis

The difference between the "constitutionally neurotic" patients and the patients with neurotic reactions is a strong one That 88 per cent of the former and only 4 per cent of the latter had abnormal capillary pictures in the nail fold is certainly significant It would seem to indicate that there is a developmental defect in the patients with con-

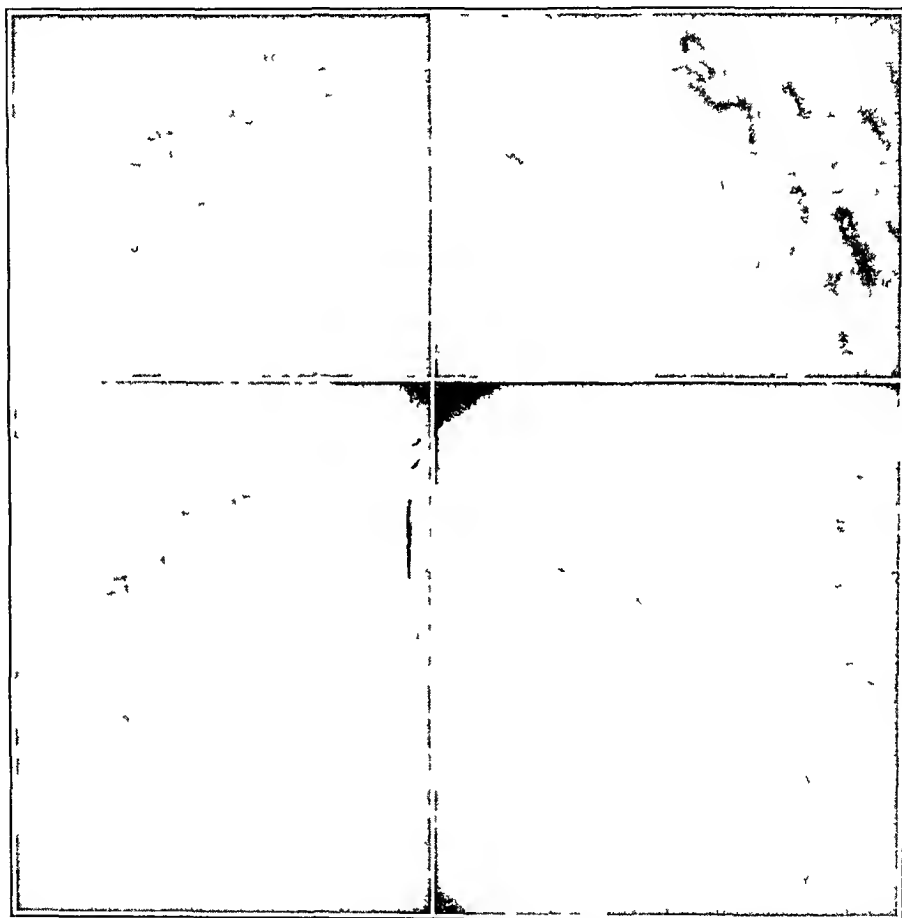


Fig 3—Abnormal tortuosities of the capillaries in constitutionally neurotic patients The pictures show different forms and degrees of abnormally shaped capillaries of the end row

stitutional neurosis which is absent in the patients classified as having only "neurotic reactions" The fact that the abnormal capillary picture is made up of peculiarly shaped capillary loops, or occasionally even of horizontal vessels, such as are seen in the early stages of normal development, indicates that the abnormality is congenital rather than acquired The findings are not surprising They merely support the conception of those authors who believe in the constitutional basis of

some neuroses and who do not believe that environmental factors always give the clue to an understanding of the neuroses. Examination of the capillary pattern might be a useful test in cases in which it is important to distinguish between anlage and morbid reaction, e g, in the examination of would-be soldiers or employees for special work which requires

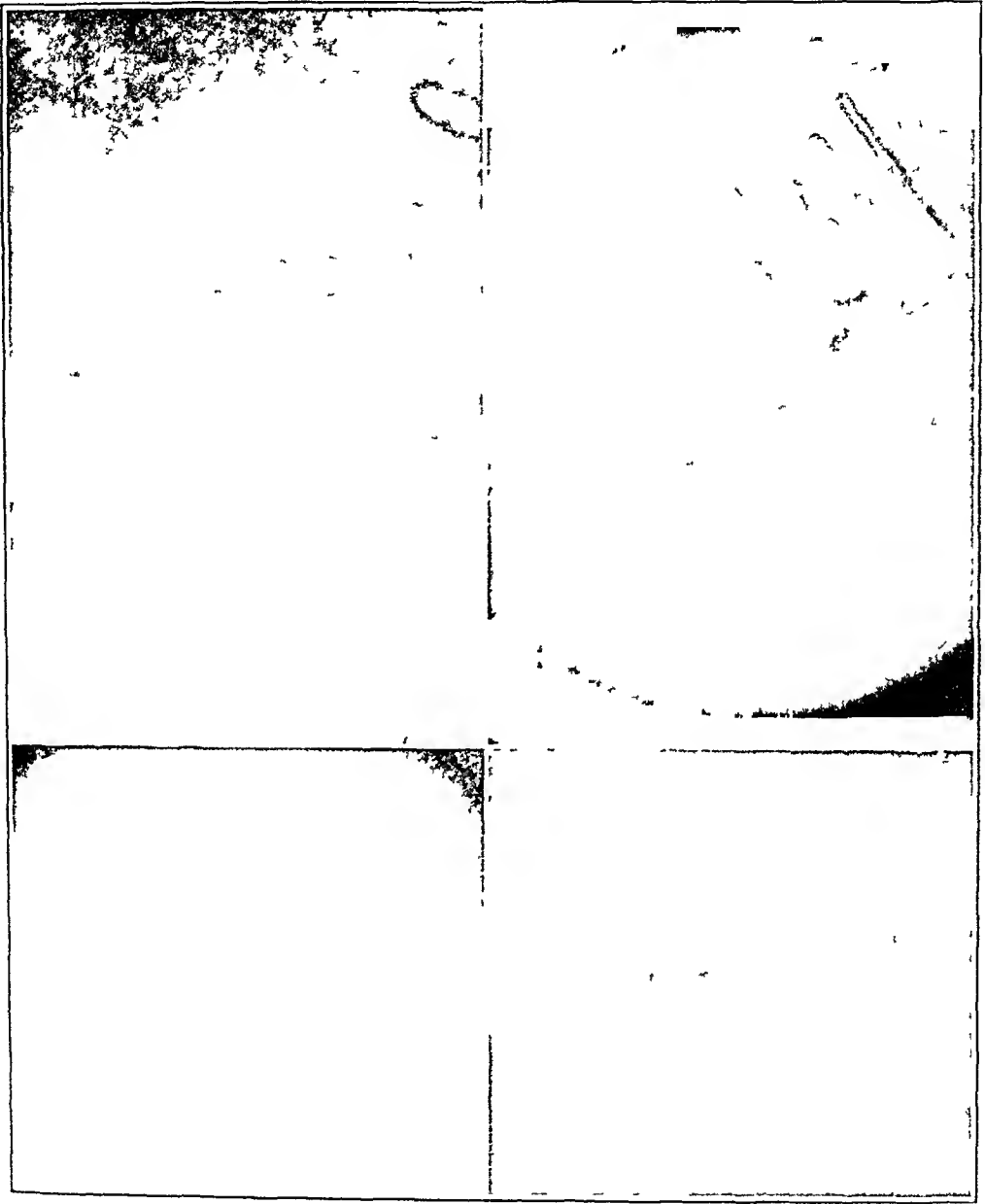


Fig 4—Immature capillary pattern in patients with idiopathic epilepsy. Horizontal vessels are visible in the more proximal rows, in *D* there is even a network of these vessels. One can follow the capillaries of the end row into these horizontal vessels.

a stable personality or in the examination of school children. The study of such objective somatic signs gives psychologic tests a broader basis.

*Epilepsy*—I examined 117 patients with epilepsy, 73 of them may be said to have idiopathic epilepsy and 44 symptomatic epilepsy. I do

not have to stress that this differentiation is often difficult, or even impossible. In most cases I also made use of the electroencephalogram. The capillary picture was characterized by horizontal vessels, or even a horizontal network, in the proximal part of the nail fold (fig 4). The capillaries of the end row did not show many anomalies. One could follow the capillaries of the end row into those horizontal vessels. It was an "immature picture," such as is seen in mentally retarded children. Further evidence was the presence of abnormally shaped capillaries, such as are seen during the early stages of normal development of the capillaries. Thus, it would seem that this pattern represents a retarded development of the capillaries or a development which came to a standstill before it was finished.

I found this capillary picture in 50 of the 73 patients with idiopathic epilepsy, that is, in 68.4 per cent. The figures for the patients with symptomatic epilepsy were quite different. Of 44, only 10 showed this picture—22.7 per cent. This is a significant difference in spite of the inevitable errors in diagnosis as to "idiopathic" and "symptomatic." One must consider the theory that even in symptomatic epilepsy there might be a specific cerebral predisposition which requires an additional exogenous factor in order to manifest itself in epileptic seizures. I do not like to say that the presence of those horizontal vessels is a positive diagnostic aid in questionable cases of epilepsy, for one can find them occasionally also in nonepileptic cases. Nevertheless, one can say that the absence of those vessels speaks strongly against idiopathic epilepsy (fig 5).

Of the few capillary studies which I found in the literature, only two authors mention observations on epileptic patients. Olkon<sup>9</sup> described epileptic monozygotic twins and spoke of "thickened walls of the subpapillary plexus." This at least can be interpreted as evidence of the visibility of such a plexus. Leader<sup>5</sup> examined 12 patients with epilepsy, in 2 she saw evidence of retarded development, namely, bizarre shapes subpapillary plexus and irregular corium. In 2 others she noted the pattern of "vasomotor instability." She did not distinguish between idiopathic and symptomatic epilepsy, but even so her observations represent some support of my own.

*Migraine*—I studied the capillary pattern of patients with migraine because of the well known relationship between epilepsy and migraine. I examined 37 such patients. In my opinion, the diagnosis of migraine is made much too often. My patients had true migraine, I believe although, of course, there might be some cases which another examiner would put in a different category of headache. The same holds true

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9 Olkon, D. M. Epilepsy of the Angiospastic Variety in Monozygotic Twins, *Arch Neurol & Psychiat* 25 1111 (May) 1931

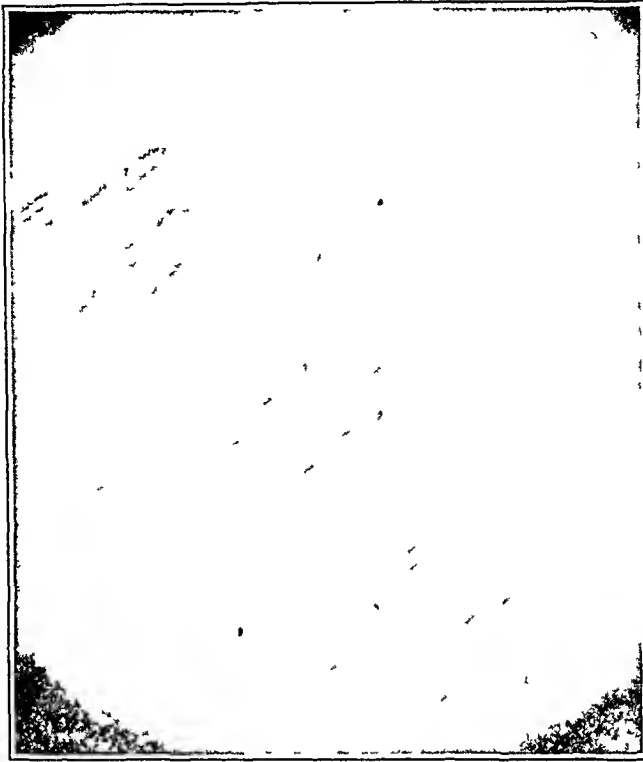


Fig 5—Normal capillary pattern in a patient with symptomatic epilepsy, showing hairpin-like, straight, evenly distributed capillaries in three rows

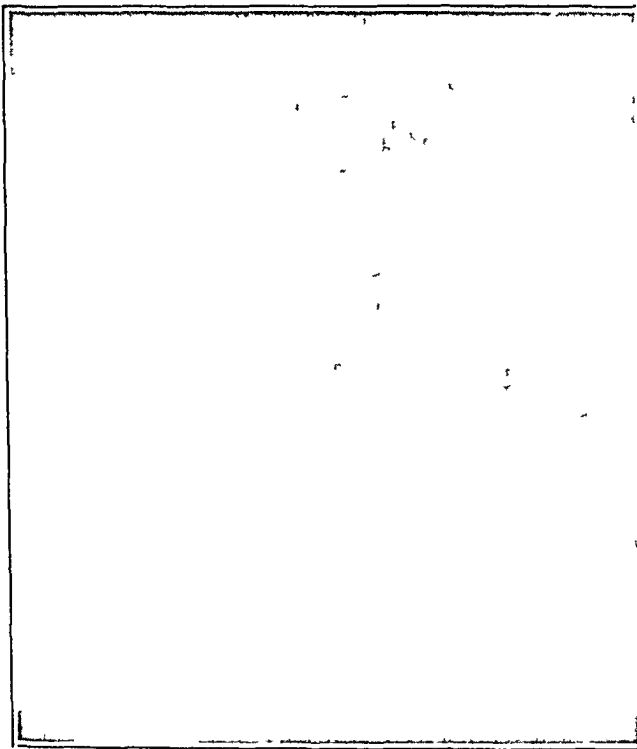


Fig 6—Immature capillary pattern in a patient with migraine, showing horizontal vessels in the proximal row, in connection with the capillaries in the end row



for the 21 patients with nonmigraine headaches, in these 21 patients the main symptom was headache. Of the 37 patients with migraine, I found a picture (fig 6) like that accompanying idiopathic epilepsy in 20, that is, in 54 per cent, whereas none of the patients with nonmigraine headache showed this capillary picture. This is in accord with the concept that migraine and epilepsy grow on the same tree. Of course, 54 per cent is a figure too low to enable one to state that migraine has a typical capillary picture, however, when it is compared with the 14 per cent of similar changes in all the other patients examined, it indicates an abnormal anlage of the capillaries of the peripheral vessels. This may be true of the brain, provided the capillary pattern of the finger nail fold permits one to draw any conclusions concerning the cerebral capillaries.

Recently, studies of the capillaries of the fingers in patients with migraine have been published by Redisch and Pelzer<sup>10</sup>. These investigations were concerned, however, with the impaired visibility of the capillaries during an attack of migraine and the effect of ergotamine tartrate, rather than the form of the capillaries.

#### SUMMARY

1 There exists a characteristic "normal" pattern of the capillaries of the finger nail fold in adult "normal" persons.

2 The immature capillary picture of the newborn develops to the mature end stage, which can be reached as early as 6 months or as late as 6 years of age.

3 This normal development is arrested at various stages in mentally retarded children.

4 Constitutionally neurotic patients showed an abnormal capillary picture, consisting mainly in tortuosities of the normally hairpin-like capillaries in 88 per cent. Patients with neurotic reactions, on the other hand, showed this picture in only 4 per cent. Therefore, examination of the capillaries furnishes a means of detecting persons of neurotic predisposition.

5 Patients with idiopathic epilepsy display an immature capillary picture, similar to that seen during the normal development of the capillaries in early childhood, before the end stage is reached. Patients with symptomatic epilepsy show this pattern to a much less degree.

6 Migrainous patients show a capillary picture similar to that of epileptic patients.

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<sup>10</sup> Redisch, W., and Pelzer, R. H. Capillary Studies in Migraine, *Am Heart J* 26: 598, 1943.

# CAPILLARIES OF THE NAIL FOLD IN PATIENTS WITH NEUROCIRCULATORY ASTHENIA (EFFORT SYNDROME, ANXIETY NEUROSIS)

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AS PART of an extensive study<sup>1</sup> of neurocirculatory asthenia, in which many methods of examination were used, the capillaries of the nail fold were examined in 48 patients with neurocirculatory asthenia<sup>2</sup> and in 44 normal controls. It has long been known that persons with peripheral vascular disease have abnormal capillaries that can be seen in the nail fold and that in certain cases of mental defect,<sup>3</sup> "vasomotor neurosis,"<sup>4</sup> epilepsy and migraine variations from the normal capillary picture occur.<sup>5</sup> Recently Hauptmann<sup>6</sup> has thoroughly reviewed the literature and has shown that in many patients with psychoneurosis, especially anxiety states and hysteria, the capillaries are abnormal. He has helped us in our study by showing us his material, by advising as to our technic and by making photographs for us.

## METHOD

With the 92 persons included in this study the usual procedure was to examine the nail fold of the fourth finger of each hand. If the cuticle was thick and the visibility bad, another finger was sometimes used. The area to be examined was lightly sponged off with an alcohol-ether mixture to remove oily deposits. Then, after the finger was placed in the holder beneath the lens, a drop of cedar oil was

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From the Massachusetts Branch of the Hall-Mercer Hospital

The work described in this paper was done under a contract, recommended by the Committee of Medical Research, between the Office of Scientific Research and Development and the Massachusetts General Hospital

1 White, P D , Cobb, S , Chapman, W P , Cohen, M E, and Badal, D W  
Tr A Am Physicians **58** 129, 1944

2 For a definition of neurocirculatory asthenia, see article cited in footnote 1

3 Potosky, C Am J Ment Deficiency **47** 167, 1942

4 Parriseus, W Deutsche Ztschr f Nervenhe **72** 310, 1921 Parriseus' figure 5 is comparable to the pattern for our normal controls and his figure 15 to the pictures for 4 patients with neurocirculatory asthenia

5 Paskind, H A, and Brown, M Constitutional Differences Between Deteriorated and Nondeteriorated Patients with Epilepsy, Arch Neurol & Psychiat **49** 49 (Jan ) 1943

6 Hauptmann, A Capillaries in the Finger Nail Fold in Patients with Neurosis, Epilepsy and Migraine, Arch Neurol & Psychiat, this issue, p 631

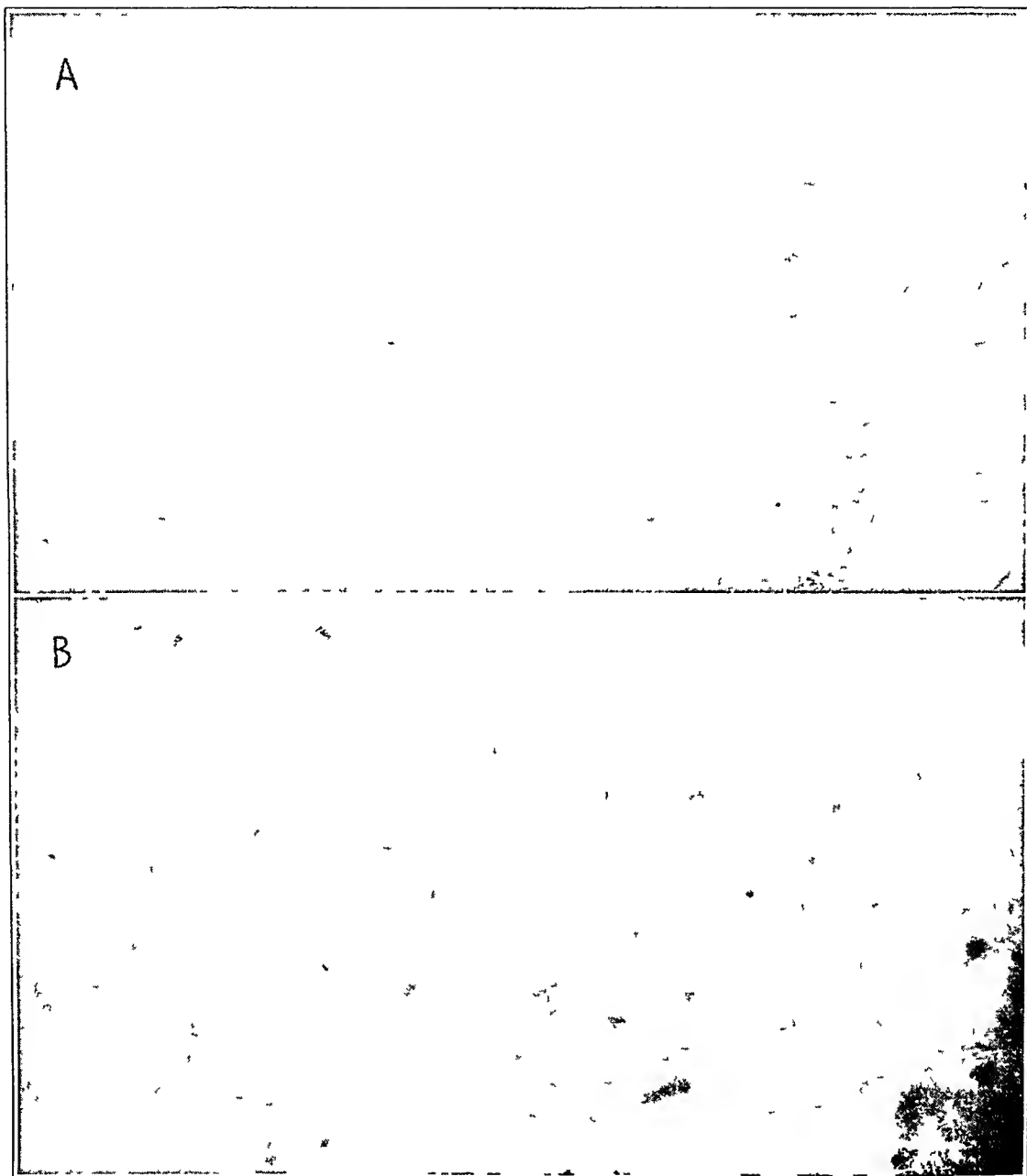
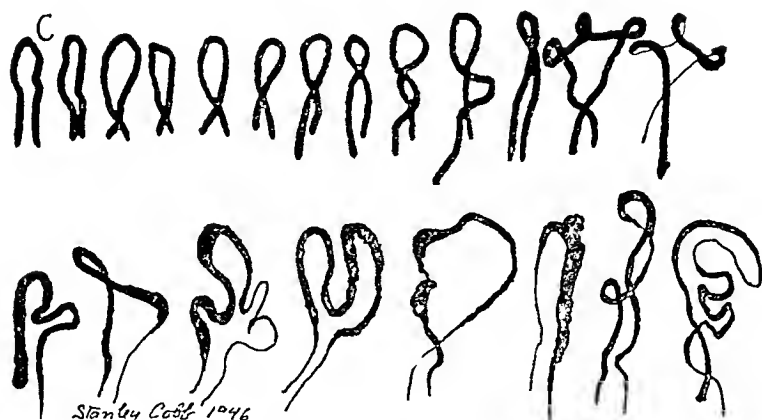


Fig 1—*A*, photomicrograph of capillaries at the edge of the nail fold of a patient with neurocirculatory asthenia. Of the 9 capillaries in focus in this plane, it can be seen that 3 are simple loops and 6 are more complex in form. Magnification, about 200.

*B*, 5 capillaries along the edge of the nail fold, 3 are simple, hairpin loops, and 2 are the more complex form described in the text.



C, drawings of capillary loops selected from several patients to show variations in form. The first 4 in the upper row would be called hairpin forms in spite of a slight crossing at the bottom. The fifth loop is equivocal, and the next 8 are definitely looped forms. The lower row shows some of the many complex forms

spread over the junction of the cuticle and the nail at a point where it seemed smooth and flat. The observations were made with a Zeiss capillary microscope with a no 8 objective and a no 6 ocular, giving a magnification of about 48 diameters. The field was illuminated with a strong, laterally directed electric lamp focused through two lenses, a water filter for coolness and a light green filter.

When the capillaries in the edge of the cuticle were brought into focus, an area was found where the outermost series of loops could be seen clearly. With averaged-sized capillaries normally spaced, one microscopic field would take in 12 to 14 loops, arranged usually in a somewhat regular row across the field. One or two such fields can be found in most nail folds, and the first good one found was used. A series of 10 capillary loops was then drawn on paper by the observer. The same procedure was followed with the other hand. The drawings were labeled and filed with the patient's record.

In making counts from these drawings, the capillaries were at first divided into morphologic types representing (a) simple, hairpin-shaped forms, (b) looped forms in which the arterial arm crossed the venous arm one or more times, making a closed loop at the end, and (c) irregular, branching forms, fanlike, ameoboid,

*Percentage Incidence of Simple Hairpin and Complex Capillary Loops in the Finger Nail Fold in 48 Patients with Neurocirculatory Disturbances and in 44 Controls*

	Simple	Complex
Patient with neurocirculatory asthenia		
-Chronic (32)	44	56
Acute (16)	47	53
Controls		
Normal (23)	79	21
Osteomyelitis (21)	65	35
Totals		
Patients with neurocirculatory asthenia (48)	45	55
Controls (44)	72	28

finger-like, etc (fig 1). After much counting and recounting, it was decided that the significant morphologic feature was the simplicity or complexity of the loops, i e, whether they were (a) simple, hairpin forms or (b) complex forms, it making no difference whether the complex forms were looped, corkscrewed, spiraled or branched. Thus, only two classes were made in the final counts. When

two or more observations were made on the same patient, the counts were averaged and the average recorded as the score for that patient. The nearest whole number was used, and if the average came out halfway between the two classes, the normal "hairpin" score was given the benefit of the tie. For example, the right hand of one subject showed 5 hairpin forms and 5 complex loops, and the left hand 4 hairpin forms and 6 complex loops in a count of 10. The average was recorded as 5 of each.

### RESULTS

From the examination of 48 patients with neurocirculatory asthenia and 44 controls, it was seen that the average percentages of hairpin and complex forms for the patients were approximately equal, whereas the controls had about 7 hairpin forms to 3 complex forms. The data are presented in the accompanying table and in figures 2 and 3.

The table is arranged with two columns, headed "Simple" and "Complex" (fig. 1 C). The figures in the first column show the average per cent of simple, hairpin forms found in the various categories listed to the left. For example, the 32 patients with chronic neurocirculatory asthenia had slightly more complex capillary loops than the 16 patients with the acute form, but the difference was too small to be significant.

The controls were of two classes, both of which showed many more simple, hairpin forms than the patients. The first group, called "normal controls," were made up of 13 men—young, vigorous Navy personnel who had been through battle and showed no symptoms. Added to these were 10 soldiers who had finished training but had not been in combat. To get a sample for control who had been living under conditions more like those of the patients with neurocirculatory asthenia, and to see whether chronic illness and convalescence were associated with abnormal capillaries, we examined 21 soldiers with osteomyelitis complicating war wounds in the wards of an Army general hospital. These patients had no neurocirculatory disorder or past history of neurocirculatory asthenia. Among their symptoms were easy fatigability, shakiness, loss of weight, anorexia and nervousness. They also showed more hairpin forms than complex forms. The average for the total control group was 72 per cent hairpin forms and 28 per cent complex forms, whereas the average for the 48 patients with neurocirculatory asthenia was 45 per cent hairpin forms and 55 per cent complex forms. This difference is 8.9 times the standard error of the difference between the two means and is a significant difference, even when corrected for the factor of small numbers.

Figure 2 presents the same data in a scattergram, or spot chart. It brings out the fact that although there is a considerable overlap between the patients with neurocirculatory asthenia and the controls as to per cent of hairpin forms, the averages, as presented in the table, do not distort the facts. This chart shows the results for all our

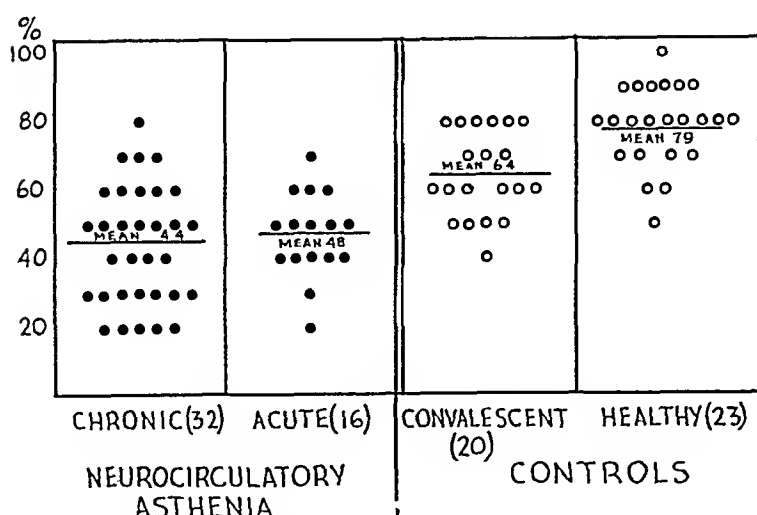


Fig 2—Percentage incidence of simple capillary loops in finger nail fold. The data used in the table are here shown on a scattergram. Each dot represents a case, and the ordinates are in percentages of simple capillary loops in each case. Thus, it is obvious that among the controls most subjects had between 64 and 79 simple, hairpin forms, whereas among the patients with neurocirculatory asthenia the greatest percentage falls between 44 and 48. It is also of interest that there is a progressive increase in the number of complex forms when the four classes are taken in sequence: healthy least, convalescent controls next, acute patients with neurocirculatory asthenia next, and patients with chronic neurocirculatory asthenia most.

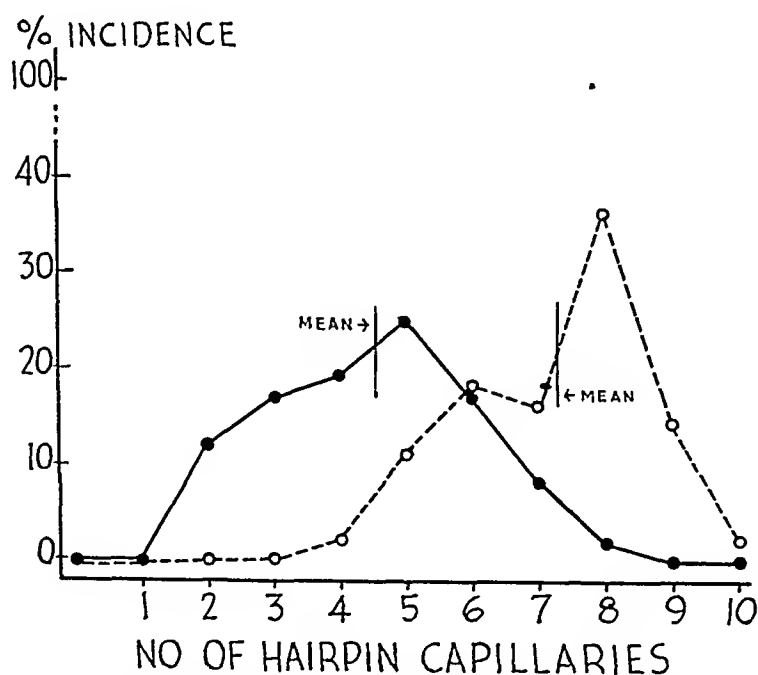


Fig 3—Chart showing number of hairpin-shaped capillary loops in 48 patients with neurocirculatory asthenia (solid line and circles) and in 44 controls (broken line and hollow circles). The numbers on the abscissa, from left to right, show hairpin forms divided into classes of 1 out of 10 capillaries, 2 out of 10, and so on, to 10 out of 10, in the last class to the right. The ordinate indicates the percentages of patients and of controls which fell in each of these classes. The data show that the controls had many more hairpin forms and, on the other hand, that the patients with neurocirculatory asthenia had many more twisted and complex forms (see text).

subjects Moreover, it indicates that there was a consistent progression from most normal to most abnormal, beginning with the normal controls and proceeding through convalescent controls and patients with acute neurocirculatory asthenia to patients with chronic neurocirculatory asthenia

The contrast between the patients with neurocirculatory asthenia and the controls is given in another way in figure 3, in which the abscissa shows the hairpin forms divided into classes of 1 out of 10 capillaries, 2 out of 10 capillaries, and so on, to 10 out of 10 capillaries The ordinate shows the percentage incidence of each of these categories

It will be noted that all the control subjects had at least 4 hairpin forms out of 10 capillaries, whereas 13 per cent of the patients with neurocirculatory asthenia had only 2 out of 10 and 18 per cent had only 3 out of 10 The mean number of hairpin forms per 10 capillaries for the patients with neurocirculatory asthenia is 4.5, whereas the mean for the controls is 7.2 This corresponds with the 45 and 72 per cent shown in the table

The peak of the curve for the patients with neurocirculatory asthenia is at 5, whereas for the controls it is at 8 In other words, the largest percentage of patients with neurocirculatory asthenia had 5 hairpin forms to 5 complex forms, whereas the largest percentage of controls had 8 hairpin forms to 2 complex capillary loops In comparing all the normal controls with all the patients, it can be said that the difference between the mean for the two groups is 2.73, and the difference between this difference and the standard error of the difference between the two means is 8.9 The odds against this observation being a chance one are more than 3.9 by  $10^{11}$  to 1

#### COMMENT

The difference in shape of the capillary loops at the edge of the nail fold in patients with neurocirculatory asthenia as compared with that in normal controls is a conspicuous phenomenon The figures previously cited, which give the standard error of the difference between the two means as 8.9, strongly support the conclusion that this is a significant difference Nevertheless, the mathematical calculations are reliable only if the original microscopic observations are reliable It is obvious that there is a subjective element in these observations The counts are made by observers who might well have a bias and would therefore choose a microscopic field that was more or less normal, thus weighting the data in one way or the other Such personal equations are impossible to eliminate, but in our opinion they are small and relatively unimportant In the first place, in the average nail fold, one can find only one or two places where the edge is even enough to give a good sequence of 10 capillaries to count Second, three observers were employed, and

in some cases two of them checked each other's counts, finding little discrepancy

Another difficulty is in judging when a capillary has a plain hairpin form and when it is to be considered a looped form. If the area observed shows a thin cuticle at the right angle to the axis of the microscope, the hairpin forms can be observed for a long distance, and eventually many of them are seen to have a twist that could cause them to be classified as "loop" forms. In most cases the capillaries can be clearly seen for only a short distance, so we classified as "loops" of complex form only those capillaries that had the twist near the top, where the arterial limb goes over to the venous (fig 1 C). Such difficulties mean that judgments have to be made and that the subjective element is not negligible.

In the table a comparison of the per cent of hairpin forms and the per cent of complex forms for normal controls and for osteomyelitis controls suggests that there might be a correlation between form of capillaries and convalescence from chronic illness. The difference between these proportions is not great, and the number of subjects is not large. However, a difference of 14 per cent is statistically significant, being 3.5 times the standard error of the difference between the means. The odds against this being a chance observation are about 1,000:1. This suggests that the irregularities found in the capillaries occur in disorders other than neurocirculatory asthenia and that they may be associated with chronic illness or with the convalescent state.

Most authors who have examined these capillaries believe that the variation is "congenital," but they give no proof.<sup>7</sup> Moreover, most of the papers neither define this term nor state their clinical diagnostic terms with enough accuracy to allow valid comparison with their data. Finally, the capillary picture associated with neurocirculatory asthenia somewhat resembles that seen in the nail fold of infants. Some authors, therefore, call these irregular loops embryonic, or primitive forms, but as yet no satisfactory proof has been brought forward that they are not the result of chronic illness. In fact, the data in the table suggest this possibility. We must conclude, therefore, that the question is unsettled and that nothing in our data answers the question as to whether the capillary abnormality is congenital or acquired after birth.

The data show that there is a variation in capillary form that correlates with neurocirculatory asthenia. This observation cannot be used as a specific diagnostic aid, because other investigators have found similar variations with "anxiety neurosis," hysteria and various clinical syndromes accompanied with vasomotor disturbances.<sup>6</sup> It is obvious that

<sup>7</sup> Griffith, J. Q., Jr. *Am J M Sc* 101:439, 1932. Potosky.<sup>8</sup> Paskind and Brown.<sup>5</sup>



more work must be done to prove whether or not the capillary picture can be varied by disease and chronic physiologic disorders. If changes can be produced, one must determine what they are like. Also, the development of the capillary loops must be followed.

#### SUMMARY

In the nail folds of 48 patients with neurocirculatory asthenia there were significantly more capillaries of complex form than in 44 normal controls. The percentages of complex forms in each class of subjects studied were as follows: normal controls, 21; convalescent controls, 35; patients with acute neurocirculatory asthenia, 53; patients with chronic neurocirculatory asthenia, 56.

The mean number of normal, hairpin-shaped forms for the patients with neurocirculatory asthenia was 4.5 out of 10 capillaries, whereas for the controls it was 7.2 out of 10.

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## ELECTROMYOGRAPHY IN DIFFERENTIAL DIAGNOSIS OF RUPTURED CERVICAL DISK

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BOSTON

THE presence of fascicular contractions in muscle is a physical sign which is of great help to the clinician in reaching a diagnosis. The electromyograph can be used as a delicate tool for the detection of fasciculations not obvious to the eye, for although in some muscles over which the subcutaneous tissue is thin fasciculations if present can be readily observed, in other muscles even when present they escape observation. In some cases the bilateral or diffuse nature of a lesion can be observed earlier by electromyography than by clinical examination.

The application of electromyography to the detection of fasciculations in muscles due to lesions of the spinal cord and of the peripheral nerves has been in use in this laboratory<sup>1</sup> and in others<sup>2</sup> for some time. In 1944 Hoefer and Guttman<sup>2</sup> described an electromyographic method for determination of the level of lesions in the spinal cord and demonstrated its usefulness in a series of 24 cases of lesion of the cord. Of these cases, 2 were of ruptured cervical disk, the level of which they were able to localize by electromyography to within one or two segments of the actual level, as verified by later operation. These authors suggested that the network of internuncial neurons in the cord may be responsible for the spread of motor unit discharges to segmental levels other than those of the lesion.

In the present study, 10 cases of suspected compression of nerve roots by protruding intervertebral disks have been reviewed in the light of their electromyographic findings. In 9 of these 10 cases, operation

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This study was aided by a grant from the National Foundation for Infantile Paralysis, Inc.

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1 Watkins, A L., and Brazier, M A B. Studies on Muscle Innervation in Poliomyelitis and Nerve Injuries, *Arch Phys Med* **26** 69-75 (Feb) 1945.

2 Hoefer, P F A, and Guttman, S A. Electromyography as a Method for Determination of Level of Lesions in the Spinal Cord, *Arch Neurol & Psychiat* **51** 415-422 (May) 1944.

was performed, and therefore confirmation of the segmental involvement was furnished by operative observation, the other case having confirmation by myelographic studies. In 2 cases of suspected ruptured disk with normal electromyograms no lesion of the disk was observed at operation. The electromyographic findings in these cases are also compared with those in cases of anterior horn cell disease in progressive muscular atrophy.

#### ELECTROMYOGRAPHIC METHOD

The same technic for recording electrical discharges from muscles was used in this work as has been described in previous work from this laboratory.<sup>3</sup> In the routine electromyographic tests on patients coming for clinical diagnosis and localization, surface electrodes have been used. In our experience, little information is lost by the substitution of surface electrodes for needle electrodes, and the ordeal is considerably less for the patient. In some cases of a bilateral lesion of the spinal cord as many as eighteen or twenty pairs of electrodes may be needed for accurate determination of the level of involvement. The advantage to the patient of the surface electrode technic is obvious in such a case. In addition, fasciculations are sometimes not recordable from the first area tested on a muscle, and many shiftings of the electrodes may be needed before the optimum site for recording is found. It is also questionable whether the introduction of the needle electrode into the body of the muscle itself may not set up some irritability and a current of injury, resulting in electrical discharges which are artefacts.

The recording units for this work were both ink-writing oscillographs, one recording from six muscles simultaneously and the other from three. In a few cases a cathode ray oscillograph was used.

#### RESULTS

For the purpose of analysis of the electromyograms, the cases of protruding intervertebral disk will be reported first.

As examples of the type of examination used and the correlation between clinical signs and electromyographic findings, 2 cases will be presented in some detail, and the other cases in this category will be tabulated later.

CASE 1—The presenting complaints in this case were pain in the neck and left shoulder and arm, with numbness of the middle finger, which was aggravated by coughing, sneezing and straining. There was tenderness over the sixth cervical spinous process. No fasciculations could be seen. Roentgenographic examination with Pantopaque<sup>4</sup> showed a large filling defect at the sixth cervical interspace on the left side. The electromyogram showed multiple spontaneous discharges consisting of clearcut, diphasic spikes occurring in some muscles but not in others.

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3 Watkins and Brazier.<sup>1</sup> Schwab, R. S., Watkins, A. L., and Brazier, M. A. B. Quantitation of Muscular Function in Cases of Poliomyelitis and Other Motor Nerve Lesions, *Arch Neurol & Psychiat* 50: 538-545 (Nov.) 1943.

4 An iodized poppyseed oil, with special cohesive properties, used as a contrast medium for myelography.

These discharges were found when the muscles were in complete relaxation. The distribution of these abnormalities may be summarized as follows:

Muscle (Left Side)	Segment	
Deltoid	C5 C6	Electromyogram normal
Biceps	C5 C6	
Extensor carpi radialis	C6 C7	Area of maximum electromyographic abnormality
Flexor carpi radialis	(C6) C7 C8	
Triceps	C7 C8 Th1	Area of electromyographic abnormality (common root C7)
Abductor pollicis brevis	C7 C8	
Abductor digiti quinti	C8 Th1	
		Electromyogram normal

It will be seen that the abnormal spontaneous discharges occurred only in those muscles served by the seventh cervical root, and therefore one would suspect compression of this nerve root.

Operation revealed a fragment of ruptured disk at the sixth cervical interspace pressing on the seventh cervical root on the left. This was removed and the nerve decompressed. Fifteen days after removal of the fragment electromyographic

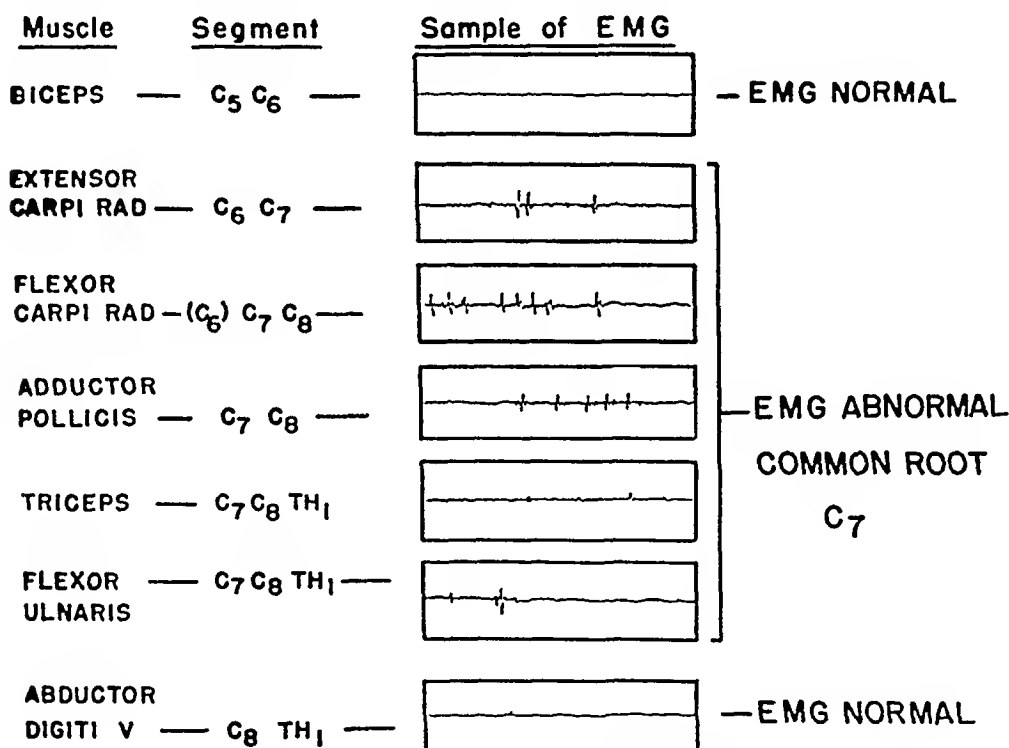


Fig 1—Electromyograms in a case of ruptured cervical disk. The maximum voltage of the highest discharge is 80 microvolts.

studies were repeated. All trace of spontaneous electrical activity had disappeared, and the only remaining abnormality was some signs of hyperirritability in the left extensor carpi radialis.

Another case is illustrated in figure 1, in which examination with a contrast medium showed a pronounced filling defect at the sixth cervical interspace on the right side consistent with a ruptured intervertebral disk pressing on the seventh cervical root on that side. The details of the case, in brief, are as follows:

CASE 2—The presenting complaints in this case were severe pain in the right shoulder and arm for two weeks, which was aggravated by coughing and sneezing.

The clinical findings were weakness of the triceps muscle and hyperesthesia of the index finger, tips of the third finger and thumb and the radial aspect of the forearm on the right side. No fasciculations could be seen. Roentgenographic studies with a contrast medium showed a filling defect at the sixth cervical interspace on the right. Although no fasciculations could be detected clinically, many were found electromyographically, with the muscle distribution shown in the following tabulation:

Muscle (Right Side)	Segment	
Biceps	C5 C6	Electromyogram normal
Extensor carpi radialis	C6 C7	Electromyogram abnormal (common root C7)
Flexor carpi radialis	(C6) C7 C8	
Adductor pollicis	C7 C8	
Triceps	C7 C8 Th1	
Flexor ulnaris	C7 C8 Th1	
Abductor digiti quinti	C8 Th1	Electromyogram normal

It will be noticed that of the eight muscles examined, including those of the hand, there were six which were served by some branch of the seventh cervical root. Each one of these six muscles when completely relaxed showed some abnormality in the electromyogram (fig. 1). The two muscles not served by the seventh cervical root gave normal electromyograms.

The rest of this series of cases of ruptured disk is summarized in the accompanying table. In all our cases with positive electromyographic evidence the seventh cervical root was the one compressed. It will be noticed that in a case in which the presence of the lesion was confirmed at operation (case 5) not only those muscles normally innervated by the seventh cervical root were electromyographically abnormal, but the biceps also. Also, in 2 cases (8 and 10) one or two muscles presumably innervated by the seventh cervical root were found to be normal. These anomalies are not surprising, since the actual innervation is not exactly known and the anatomic distribution may vary in different persons.

Of interest in view of these results are the findings in 2 cases in which exploratory laminectomies were done but ruptured disk was not found.

**CASE 11**—The patient entered the hospital complaining of pain in the left arm and the left side of the neck, this had been present for six months but recently had increased in intensity and was now unbearable. There was no atrophy or paresthesias. Studies of the cervical portion of the spine with a contrast medium showed normal interspaces, although equivocal roentgenographic findings suggested to some observers that compression of the sixth or seventh cervical nerve root might be the cause of the pain. A laminectomy was therefore performed, but no compression of the nerve roots was observed and exploration revealed no abnormality. The final diagnosis was fibrositis due to rheumatoid arthritis.

In this case the electromyogram before operation was also normal. The deltoid, biceps, triceps and extensor and flexor carpi radialis muscles were all normal on the left side, with no spontaneous activity at rest.

**CASE 12**—The patient complained of pain in the neck and the left arm with some weakness of that arm. There was a history of several accidents. Studies with a contrast medium showed signs suggestive of a lesion at the sixth cervical interspace. A hemilaminectomy was therefore performed on the left, but no pro-

truding intervertebral disk was seen. The electromyogram before operation revealed no abnormalities in any muscle distribution. The subsequent course in this case made it clear that the diagnosis was that of brachial neuritis.

*Electromyographic Findings in Cases of Ruptured Cervical Disk*

Case No	Muscles with Abnormal Electromyogram	Muscles with Normal Electromyogram	Localization by Myelogram	Localization by Operation	Compressed Root
1	Extensor carpi radialis C6 C7 Flexor carpi radialis (C6) C7 C8 Abductor pollicis brevis C7 C8 Triceps C7 C8 Th1	Deltoid C5 C6 Biceps C5 C6 Abductor digiti V C8 Th1	C6 inter-space	C6 disk	C7
2	Extensor carpi radialis C6 C7 Flexor carpi radialis (C6) C7 C8 Adductor pollicis C7 C8 Triceps C7 C8 Th1 Flexor ulnaris C7 C8 Th1	Biceps C5 C6 Abductor digiti V C8 Th1	C6 inter-space		C7
3	Extensor carpi radialis C6 C7 Flexor carpi radialis (C6) C7 C8 Opponens pollicis C7 C8	Trapezius C1 C4 Deltoid C5-C6 Biceps C5-C6 Triceps C7 C8 Th1 Abductor digiti V C8 Th1	C6 inter-space	C6 disk	C7
4	Triceps C7 C8 Th1	Deltoid Biceps	C6 inter-space	C6 disk	C7
5	Biceps C5 C6 Extensor carpi radialis C6 C7 Triceps C7 C8 Th1	Deltoid C5 C6	C6 inter-space	C6 disk	C7
6	Extensor carpi radialis C6 C7 Triceps C7 C8 Th1	Deltoid C5 C6 Biceps C5 C6 Abductor digiti V C8 Th1	C6 inter-space	C6 disk	V7
7	Triceps C7 C8 Th1	Deltoid C5 C6 Biceps C5 C6	C6 inter-space	C6 disk	C7
8	Extensor carpi radialis C6 C7 Flexor carpi radialis (C6) C7 C8	Trapezius C1 C4 Deltoid C5 C6 Biceps C5 C6 Triceps C7 C8 Th1 Opponens pollicis C7 C8	C6 inter-space	C6 disk	C7
9	Extensor carpi radialis C6 C7 Triceps C7 C8 Th1	Trapezius C1 C4 Deltoid C5 C6 Biceps C5 C6	C6 inter-space	C6 disk	C7
10	Extensor carpi radialis C6 C7 Adductor pollicis C7 C8 Triceps C7 C8 Th1	Deltoid C5 C6 Biceps C5 C6 Abductor pollicis brevis C7 C8		C6 disk	C7
11	None	Deltoid C5 C6 Biceps C5 C6 Extensor carpi radialis C6 C7 Flexor carpi radialis C6 C7 C8 Triceps C7 C8 Th1	Questionable	None found	None
12	None	Deltoid C5 C6 Biceps C5 C6	Questionable C5	None found	None

COMMENT

To the electromyographer there are certain differences in the recordings obtained from muscles in cases of root compression and those in cases in which there is a degenerative process of the anterior horn cell.

as in progressive muscular atrophy. An electromyogram from 1 of a series of 20 cases of this disease is shown in figure 2. The muscle distribution of abnormalities is, of course, different in these cases because the findings are often bilateral and may occur in the muscles of all four extremities. In the early stage the fasciculations are often not visible to the eye and can be demonstrated only by the electromyograph. Frequently cases are met with in which the only visible fasciculations are in the tongue, but the electromyograph may be able to detect them in the musculature of the trunk and limbs.

Besides the more diffuse distribution of the abnormalities in these cases there are some differences in the pattern of the electrical discharges which are found to be constant. Although less information about the actual electrical event taking place in the muscle can be deduced from surface electrodes than from coaxial needle electrodes, some constantly occurring features are of interest.

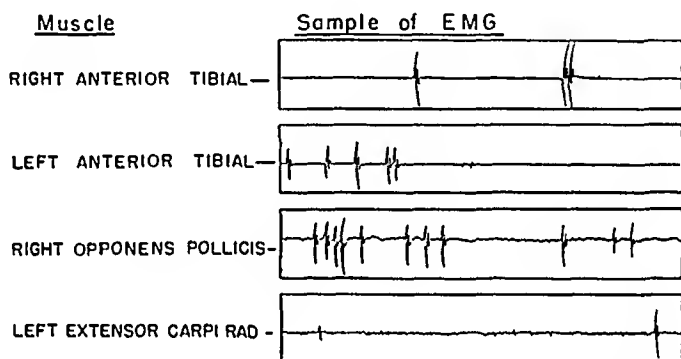


Fig 2—Electromyograms in a case of progressive muscular atrophy. The maximum voltage of the highest discharge is 250 microvolts.

In cases of progressive muscular atrophy or amyotrophic lateral sclerosis the voltage is almost invariably higher than in cases of root compression. Voltages of 250 microvolts are commonly met with, whereas in cases of axonal lesions, such as root compression and the neuritides, the discharges rarely reach this level. In the latter cases, however, the discharges from any given muscle tend to be even in voltage, repeating themselves with the same height of excursion. In cases of progressive muscular atrophy, on the other hand, they vary in voltage in a completely unpredictable way; in fact, the outstanding characteristics of these discharges are their irregularity of voltage, of grouping and of rhythm. No set rhythm of discharge is found, and the grouping is so irregular that the spikes may occur singly, or in twos and threes or in multiple groups. The spikes themselves are rather different from those found in cases of root compression, which tend to be almost purely diphasic, with perhaps some repetition of low voltage, but in cases of

progressive muscular atrophy they are usually polyphasic, with one spike of maximal voltage placed in the center of others of lesser voltage

As has already been mentioned, any explanation of the processes underlying these formations would be pure conjecture, since surface electrodes were used, but some features recur so constantly that conjecture is tempting. For example, the repetitive spikes of lower voltage and even excursion are found in many cases in which an inflammatory or irritative condition of the peripheral axon is present, as in peripheral neuritis, and in these cases of ruptured cervical disk in which electromyographic abnormalities are found it is likely that these discharges are due not so much to impaired conduction as to irritation of the nerve fibers. Grundfest<sup>5</sup> has shown that conduction in nerve fibers is normal even under immense pressure. On the other hand, in cases of progressive muscular atrophy and amyotrophic lateral sclerosis, and of hematomyelia and syringomyelia, in which the anterior horn cell is involved, the repetitive discharges of steady low voltage, so typical of irritation of the peripheral nerve, are rarely found, and if present at all are less persistent.

None of these findings need be confused with the discharges of true fibrillation of denervation, which presumably originate in the sarcolemma. The fibrillations of denervated muscle fibers are of low voltage and short duration (1 to 2 milliseconds) and are not recordable by the ink-writing oscillograph generally used in this work. Their swiftness of phase change necessitates the use of a cathode ray oscillograph. It is for this reason that the term "fasciculations" is specifically used throughout this paper.

The electromyographic details outlined here have proved in practice to be of considerable aid in the differential diagnosis of early anterior horn cell disease and lesions of the spinal root. The present report has laid emphasis on cases of ruptured cervical disk, the clinical diagnosis of these cases has been fully covered by Michelsen and Mixer,<sup>6</sup> who pointed out that the clinical detection and exact distribution of the motor deficit in these cases are indefinite because severe pain interferes with a detailed examination. It is in respect to this problem that the electromyogram takes its place as a diagnostic aid to the localization of ruptured cervical disk. Studies are being made for the application of these methods to the localization of ruptured lumbar disks.

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<sup>5</sup> Grundfest, H., in Cold Spring Harbor Symposia on Quantitative Biology, Cold Spring Harbor, L. I., New York, The Biological Laboratory, 1936, vol. 4, p. 179.

<sup>6</sup> Michelsen, J. J., and Mixer, W. J. Pain and Disability of Shoulder and Arm Due to Herniation of the Nucleus Pulposus of Cervical Intervertebral Discs of the Lower Cervical Spine, *New England J. Med.* **231**: 279-287 (Aug. 24) 1944.



## SUMMARY

The electromyographic findings are reviewed in 10 cases of ruptured cervical disk, in 9 of which operation was performed

In 2 suspected cases of ruptured disk with normal electromyograms no lesion was observed at operation

The features of the electromyograms found in cases of irritation of the nerve root by compression are contrasted with those in cases of anterior horn cell disease

## DELIRIUM

### IV Quantitative Electroencephalographic Study of a Case of Acute Arsenical Encephalopathy

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JOHN ROMANO, M D

AND

LEON GOLDMAN, M D

CINCINNATI

IN STUDIES of the effects of anoxia, hypoglycemia and alcohol on the normal electroencephalogram and the correlation of these changes with the degree of reduction of consciousness, we emphasized the fact that the degree of change in frequency in the electroencephalographic record may be of more importance than the appearance of any particular wave frequency<sup>1</sup>. Thus several subjects experiencing comparable reduction in consciousness when exposed on different occasions to anoxia, hypoglycemia and alcohol all showed the same degree of slowing in the electroencephalogram, although the final mean frequency varied widely among the different subjects, depending on the initial mean frequency. With the rather mild disturbance in consciousness induced in these experiments, abnormally slow waves (7 per second or less) appeared only in those instances in which the control records were in the slow normal range. In contrast, the subject with an abnormally fast record (mean frequency, 12.87 cycles per second) had during gross alcoholic intoxication a considerably more "normal" record (mean frequency, 9.72 cycles per second).

In the experiments just cited the effects were acute and of brief duration, and the cerebral disturbance was of mild intensity and of a high degree of reversibility once the noxious factor was removed. It is of both practical and theoretic importance to establish the validity of this principle under conditions more likely to be encountered clinically. In our earlier studies of delirium we were able to follow grossly abnormal electroencephalographic patterns back to normal but never had the

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From the Departments of Psychiatry and Dermatology, University of Cincinnati College of Medicine, and Cincinnati General Hospital.

1 (a) Engel, G. L., and Rosenbaum, M. Delirium. III. Electroencephalographic Changes Associated with Acute Alcoholic Intoxication. *Arch. Neurol. & Psychiat.* **53**: 44 (Jan.) 1945. (b) Engel, G. L., Webb, J. P., and Ferris, E. B., Jr. Quantitative Electroencephalographic Studies of Anoxia in Humans. Comparison with Acute Alcoholic Intoxication and Hypoglycemia, *J. Clin. Investigation* **24**: 691 (Sept.) 1945.

opportunity to study the electroencephalogram before the development of the delirium<sup>2</sup> In the case of acute arsenical encephalopathy here reported electroencephalograms were obtained immediately before and during the acute reaction This was an incidental observation during a study of the toxicity of Melarsen, a pentavalent arsenical compound (sesquisodium salt of N-(*p*-arsonophenyl)-melamine) This compound contains 20.9 per cent arsenic<sup>3</sup>

CASE 1—K, a 26 year old married woman, was found to have a positive Wassermann reaction of the blood in May 1943 Six years before she had delivered a 7 month premature child, who had since been found to have congenital syphilis She received one injection of a bismuth preparation and two intravenous injections of neoarsphenamine at weekly intervals After the second injection of the arsenical compound a rash developed, which lasted three days In August 1943 she received one injection of mapharsen, after which she had generalized edema, nausea, and vomiting, but no rash In November 1943 she was again examined and was found to have positive Wassermann reactions of the blood and cerebrospinal fluid, she was referred to the hospital for therapy

Physical examination revealed a well developed and well nourished woman with no abnormalities The neurologic and mental status was normal

The Wassermann reaction of the blood was positive The blood and urine were normal The cerebrospinal fluid was clear and colorless and contained a trace of globulin and 18 white blood cells per cubic millimeter (no differential count was made) The Wassermann reaction was 4 plus and the colloidal gold curve 3355521000 The diagnosis was asymptomatic neurosyphilis

The patient received 0.5 Gm of Melarsen intravenously on Dec 11 and 16, 1943 She complained of nausea and vomited once after the first injection After the second injection she experienced malaise and a rise in temperature to 100.5 F On December 20 a third injection was given After this there developed a pruritic, scarlatiniform rash, most pronounced on the trunk, general malaise, aching in the extremities, with marked muscular tenderness, nausea and frequent emesis, slight generalized edema, generalized lymphadenopathy of a mild degree, and low grade fever (99 to 101 F) She complained of severe headache and vertigo on movement of the head Neurologic examination revealed no changes from the previous condition The patient was drowsy and inattentive, and examination of the mental status revealed evidence of increased fluctuation of the level of awareness

At the height of the reaction, the urine showed a trace of albumin, with occasional red cells and white cells, and the cerebrospinal fluid contained 72 white cells per cubic millimeter (differential count not made), and a total protein of 110 mg per hundred cubic centimeters

Severe symptoms continued for five days and then gradually subsided over the course of ten days A lumbar puncture repeated six days after the one indicated in the preceding paragraph revealed an initial pressure of 90 mm of

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2 Romano, J, and Engel, G L Delirium I Electroencephalographic Data, *Arch Neurol & Psychiat* **51** 356 (April) 1944 Engel, G L, and Romano, J Delirium II Reversibility of the Electroencephalogram with Experimental Procedures, *ibid* **51** 378 (April) 1944

3 Melarsen was furnished by Parke, Davis & Company, Detroit This work was done in part under a grant from Parke, Davis & Company

water, 58 white cells (94 per cent mononuclears) per cubic millimeter and a total protein of 23 mg per hundred cubic centimeters. All specimens of the spinal fluid gave a positive Wassermann reaction. The patient was seen several months after her discharge from the hospital. There were no abnormal findings, but the serologic reactions of the blood were still positive. Penicillin therapy was recommended to her physician.

*Electroencephalographic Studies* (figure)—The method of analysis was that previously described<sup>1b</sup>. All analyses were made on the tracing from the left fronto-occipital area.

December 11. Tracings were taken before, during and two hours after the first intravenous injection of 0.5 Gm of Melarsen. These revealed a fairly regular pattern, with a dominant frequency of 11 to 12 cycles per second and a mean frequency of 11.51 to 11.53 cycles per second. The three records were similar.

December 24. This record was taken at the height of the sensitivity reaction. It revealed a much less regular and a generally slower rhythm, the mean frequency on analysis of the tracing from the fronto-occipital area being 9.12 cycles per second (range, 7 to 12 per second). The slowing was greater in the frontal areas, where occasional 6 per second waves were noted, rarely appearing in bursts.

December 31. The patient was recovering but still exhibited mild symptoms. The record showed a more regular and faster rhythm but had not as yet returned to the control pattern. The mean frequency was 10.69 cycles per second.

#### COMMENT

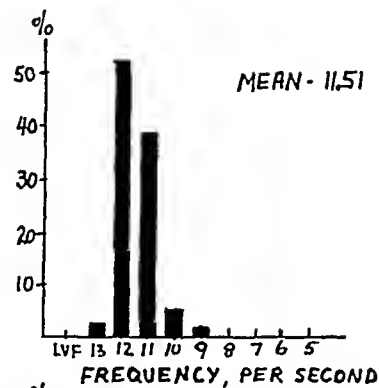
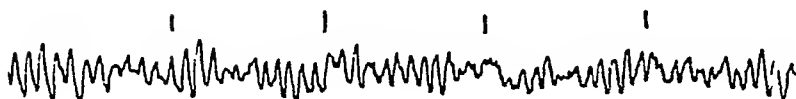
From the previous history it is apparent that this patient was sensitive to trivalent arsenic. At the initial examination she presented no physical signs or symptoms of active syphilis and was regarded as having asymptomatic neurosyphilis. Examinations of the neurologic and mental status revealed no significant abnormalities. The electroencephalogram taken before treatment was normal, and a record taken during and two hours after the first injection of Melarsen (0.5 Gm intravenously) revealed no changes, indicating that there was no direct or immediate effect of the drug on the electroencephalogram. The check in the mean frequencies also gives an indication of the reproducibility of the frequency count. Similar studies on 3 other patients also failed to reveal any immediate effect of injections of amounts up to 1 Gm of Melarsen intravenously.

The reaction began two to three days after the first injection and reached its peak after the third injection. The syndrome, characterized by fever, nausea, vomiting, generalized edema, albuminuria, scarlatiniform eruption, pruritus, myalgia, generalized lymphadenopathy, headache and mild delirium, with increased protein and cells in the cerebrospinal fluid, was of the serum sickness type of drug hypersensitivity<sup>4</sup>. It has not been common for patients to be sensitive to both trivalent and pentavalent organic arsenicals.

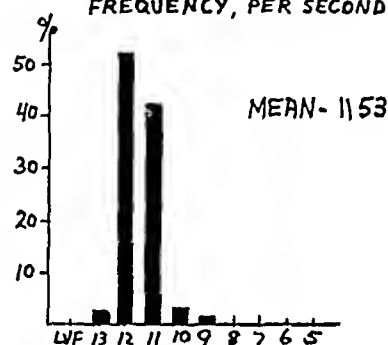
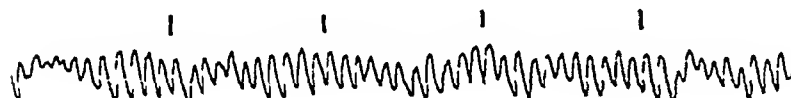
<sup>4</sup> Longcope, W. T. Serum Sickness and Analogous Reactions from Certain Drugs, Particularly the Sulfonamides, *Medicine* **22**: 251 (Sept.) 1943.

## ACUTE ARSENICAL ENCEPHALOPATHY

12/11/43 10 45 AM  
CONTROL

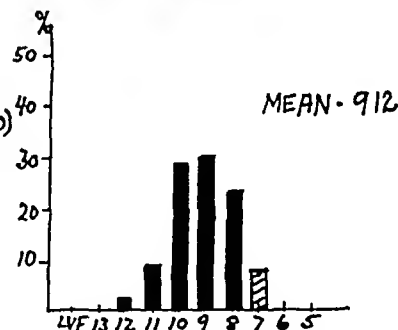
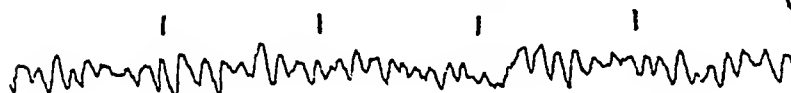


12/11/43 12 50 PM  
2 HOURS AFTER MELARSEN (0.5gm) IV



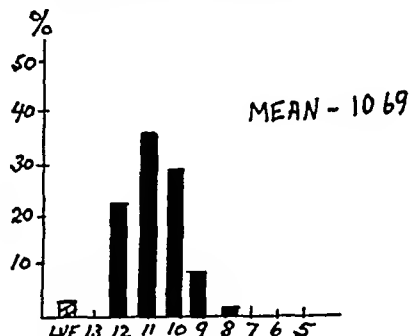
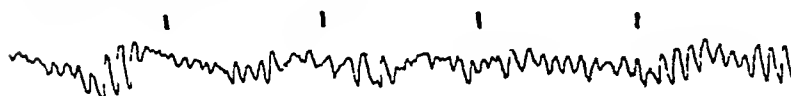
12/24/43

HEADACHE, NAUSEA, VOMITING, SKIN ERUPTION, FEVER, CONFUSION (MILD)



12/31/43

MILD SYMPTOMS STILL PRESENT



Electroencephalographic changes during acute arsenical encephalopathy  
See text for description

The magnitude of the pathologic changes in the central nervous system in this case is unknown, but they must have been minor, since the mortality in cases of severe arsenical encephalopathy is high. Roseman and Aring<sup>5</sup> emphasized the essential vascular origin of the pathologic changes in the central nervous system, with the swelling of the vascular endothelium, and often occlusion, of the small vessels. Perivascular necrosis occurs in relation to the alterations in the small vessels. The nonspecific findings of so-called vasoparalysis have also been noted.<sup>6</sup> These vascular lesions are obviously generalized, and not confined to the central nervous system.<sup>1</sup>

In our patient the arsenical medication was discontinued at a time when the reaction was still readily reversible. The diffuse endothelial swelling very likely altered the exchange of gases, substrate and electrolytes between the blood stream and the parenchyma of the brain, leading to interference with cellular metabolism and perhaps to changes in the cell membrane. Products of the local vascular inflammatory reaction, with resultant edema, may also have contributed.

The magnitude of this effect could be estimated by the quantitative change in the mean frequency in the electroencephalogram, which was of the same order as the frequencies observed in our earlier experiments with acute alcoholic intoxication.<sup>1a</sup> The degree of change in consciousness was roughly comparable. It is noteworthy that the electroencephalographic pattern at the time of maximum change would still be considered only in the category of borderline abnormal, yet the change from the control record was considerable. On inspection, the only feature likely to attract attention was the presence of occasional 6 per second waves in the frontal area. There was definite, but not striking, loss of regularity. If a control record had not been available, the significance of this electroencephalographic feature might easily have been overlooked.

Thus, when a "normal" record is obtained on a patient who manifests some disturbance in consciousness of recent and acute origin, it cannot be considered normal for the particular subject until a record is obtained after recovery and some estimate of the degree of change can be made.

#### SUMMARY

Quantitative electroencephalographic studies were carried out on a patient who manifested an acute reaction to a pentavalent arsenical compound, Melarsen. The patient was known to be sensitive to trivalent arsenic and exhibited a reaction of the serum sickness type, with

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<sup>5</sup> Roseman, E, and Aring, C. D. Encephalopathy Following Neoarsphenamine Therapy, *New England J. Med.* **224** 550 (March 27) 1941.

<sup>6</sup> Scheinker, I. M. Genesis of Encephalopathy Due to Arsphenamine (Central Vasoparalysis Due to Arsphenamine), *Arch. Path.* **37** 91 (Feb.) 1944.

evidence of mild diffuse encephalopathy. The electroencephalograms obtained before and two hours after the first injection of the arsenical drug were normal and yielded a mean frequency of 11.51 to 11.53 cycles per second. The record at the height of the reaction was only "borderline abnormal." It revealed a slowing in mean frequency to 9.12 cycles per second, but there were only rare waves of a frequency less than 7 per second. This study, again, emphasizes the importance of the degree of change in the electroencephalogram rather than the appearance of any particular wave frequency.

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# CHRONIC PSYCHOSES AND ADDICTION TO MORPHINE

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AND

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THE PSYCHOSES attributed to the use of morphine may be classified as follows (1) chronic psychoses due to habitual use, (2) psychoses due to withdrawal, and (3) psychoses due to idiosyncrasy

At the United States Public Health Service Hospital, Lexington, Ky, which is devoted primarily to the treatment of drug addiction and at which this study was made, there has been little experience with the last type (psychoses due to idiosyncrasy), since the patients are addicts and therefore habitually use large doses of morphine. However, it has been stated that this type of psychosis does occur<sup>1</sup> but is rare and occurs more frequently in women. It is characterized by excitement or delirium. Psychoses due to withdrawal constitute a separate problem.

This study is concerned with an evaluation of the first type, chronic psychoses due to habitual use of morphine. "Psychoses due to opium or its derivatives" is listed in the "Standard Nomenclature of Diseases"<sup>2</sup>. These psychoses are described in the "Statistical Manual," published by the National Committee for Mental Hygiene,<sup>3</sup> as "psychotic reactions appearing in the habitual users of opium and particularly its derivative morphine. Such effects appear to show themselves in mental deterioration with demonstrable memory defect as well as ethical and social deterioration."

Von Krafft-Ebing,<sup>4</sup> Edmunds and Gunn,<sup>5</sup> Lambert,<sup>6</sup> Bell<sup>7</sup> and Sandoz<sup>8</sup> all expressed the opinion that the habitual use of morphine

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1 Goodman, L, and Gilman, A. Pharmacological Basis of Therapeutics, New York, The Macmillan Company, 1941. Bastedo, W A. Materia Medica, Pharmacology and Therapeutics, Philadelphia, W B Saunders Company, 1934

2 Standard Nomenclature of Disease, edited by E P Jordan, Chicago, American Medical Association, 1942, p 100

3 Statistical Manual for Use of Hospitals for Mental Diseases, ed 7, New York, The National Committee for Mental Hygiene, 1936

(Footnotes continued on next page)



causes this type of psychosis Von Krafft-Ebing<sup>4</sup> stated "In severe cases we find weakness of memory and occasionally visual hallucination" Edmunds and Gunn<sup>5</sup> wrote "Eventually melancholia and dementia may follow the long use of opium and especially of morphine" Lambert<sup>6</sup> stated "Considering the symptoms, memory is one of the faculties first affected and the amnesia is similar to the beginning of senile dementia" On the other hand, many authors have questioned the statement that the habitual use of morphine causes a psychosis Among these were Dana,<sup>9</sup> Chotzen,<sup>10</sup> Schneider<sup>11</sup> and Kolb<sup>12</sup> The last-mentioned states

Intellectual deterioration is apparently never due to the use of an opiate alone Cocaine is a much more injurious drug, and it seems that most of those who have deteriorated have used both an opiate and cocaine

There is no destruction of protoplasm such as follows prolonged excessive use of alcohol Neither nerve cells nor fibers degenerate, consequently the drug cannot produce diseases analogous to Koraskoff's psychosis, acute hallucinosis, or alcoholic multiple neuritis

If opium and its derivatives cause psychoses, one would expect the incidence of psychoses to be higher among addicts than in a comparable group of nonaddicts Of approximately 600 male prisoners with addiction to morphine in this institution at the time of writing, 13, or 2 per cent, are classified as psychotic The average length of sentence for the 600 patients is two and a half years Using the data of Hobhouse and Brockway,<sup>13</sup> the incidence of psychoses in prisoners with the same average length of sentence who are not addicts would be approximately

4 von Krafft-Ebing, R Textbook of Insanity, Philadelphia, F A Davis Co., 1905

5 Edmunds, C W, and Gunn, J A, in Cushman, A R A Textbook of Pharmacology and Therapeutics, Philadelphia, Lea & Febiger, 1936

6 Lambert, A Intoxicants and Narcotics, in Nelson's New Loose-Leaf Medicine, New York, Thos Nelson & Sons, 1920, vol 2, p 555

7 Bell, M Morphinism and Morphinomania, New York M J 93 680, 1911

8 Sandoz, C E Report on Morphinism to the Municipal Court of Boston, J Am Inst Criminol 13 10, 1922

9 Dana, C L Problems of Drug Addiction, M Rec 93 177, 1918

10 Chotzen, F Zur Kenntnis der Psychosen der Morphiumabstinenz, Allg Ztschr f Psychiat 63 786, 1906

11 Schneider, K Zur Frage der chronischen Morphinpsychose und des Zusammenhangs von Sinnestauschungen und Wahnideen, Ztschr f d ges Neurol u Psychiat 19 25, 1913

12 Kolb, L Pleasure and Deterioration from Narcotic Addiction, Ment Hyg 9 699, 1925

13 Hobhouse, S, and Brockway, A F English Prisons Today, London, Longmans, Green & Co, 1922, pp 520-529

2 per cent<sup>14</sup> This indicates that there is not an increased incidence of psychoses in persons with addiction to morphine

In an effort to find changes which might be termed characteristic of a morphine psychosis, 19 morphine addicts with chronic psychoses following withdrawal of the drug were examined during the course of one year They had used morphine habitually, a few had occasionally used dihydromorphinone hydrochloride (Dilaudid), Pantopon (a proprietary preparation containing the total opium alkaloids), opium, diacetylmorphine (heroin) or cocaine The diagnoses for these 19 patients are given in table 1, they fall into the usual categories Four patients had an organic type of intellectual deterioration Two of these men had dementia paralytica, 1 had been chronically alcoholic for forty years, and another's disease was diagnosed as psychosis with cerebral arteriosclerosis

TABLE 1—*Chronic Psychoses in Patients Addicted to Morphine*

	Number of Patients	Average Length of Addiction, Years
Schizophrenia	9	20
Paranoid type	7	20
Mixed type	2	21
Dementia paralytica	2	23
Psychoses with organic disease of brain	1	31
Psychoses with cerebral arteriosclerosis	1	5
Psychoses with epilepsy and traumatic damage to brain	1	24
Alcoholic deterioration	1	40
Psychoses with mental deficiency	1	14
Psychoses with psychopathic personality	1	12
Paranoid condition	2	14
	19	20

One schizophrenic patient expressed guilt feelings concerning the use of narcotics and other antisocial acts Accusing voices told him to stop these practices Another patient with schizophrenia stated that voices asked him in a friendly manner when he was going to stop using morphine A third patient, given a diagnosis of schizophrenia prior to the use of narcotics, had a persecutory delusional system and auditory hallucinations concerning morphine, narcotic agents and the

14 Hobhouse and Brockway found that the ratio of psychoses to the number of sentences increases with the length of the sentence imposed In sentences under one month the incidence is less than 0.01 per cent This rate rises to 0.07 per cent for sentences of three months and continues to increase much more rapidly than the length of the sentence Prisoners sentenced for one year have a rate of 0.4 per cent, those sentenced for five years, a rate of 3.8 per cent and those sentenced to twenty years, a rate of 24 per cent With these data, it was determined by interpolation that the incidence of psychoses corresponding to a sentence of 25 years would be approximately 2 per cent

government In these patients, however, ideas concerning narcotics formed only a small fraction of their total abnormal thought content It appeared that these ideas were not peculiar to a morphine psychosis but, rather, were incidental to the fact that the existence of these psychotic patients was largely concerned with the procuring and using of narcotics, ideas concerning narcotics were simply woven into typical schizophrenic delusions and hallucinations

Except for occasional concern with narcotics, as already indicated, the delusions and hallucinations of these 19 patients were not unusual for the diagnoses listed The general behavior, stream of talk, affect, sensorium and insight were likewise not unusual Memory defects and deterioration were compatible with these diagnoses No features peculiar to a morphine psychosis were found

The Rorschach test was given to 6 men addicted to morphine who had a clinical diagnosis of schizophrenia Patterns indicative of schizophrenia were found The records were characterized by extreme variation in form quality of the responses, one of the most reliable signs of schizophrenia Contamination, which is found in adults only among schizophrenic persons,<sup>15</sup> appeared in 3 of the 6 records Whole responses increased, together with a decrease in their quality Confabulatory wholes were present in 2 records The number of M responses was decreased for all records The M to C ratio showed a domination of color over movement All the records were high in CF and C responses, with few, if any, FC responses Abstract and personal references occurred frequently

The Rorschach factors correlated with the clinical findings Failure of the patient's control was shown in the lower percentage of F+ responses or in a high percentage of F responses with a large number of F— responses Absence of differentiated shading (FK or Fc) also indicated this lack of control The inability of the schizophrenic patient to handle everyday situations as a result of his lack of contact with reality, together with his futile though ambitious attempts to achieve recognition, was shown in the approach, which was characterized by crude or confabulated wholes and a lack of D responses Attention to tiny details, representing preoccupation with inconsequential and unimportant things, was found The lack of human movement responses corresponds to a lack of constructive inner life Blocking was shown in a rejection of cards and in application of abstract and personal references

Because it has been stated<sup>3</sup> that in the psychoses due to opium and its derivatives there is a "mental deterioration with a demonstrable memory defect," special attention was given this aspect of the problem

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15 Klopfer, B, and Kelley, D The Rorschach Technique, Yonkers-on-Hudson, N Y, World Book Company, 1942, p 354

The Shipley-Hartford Retreat Scale<sup>16</sup> was used in this study for the measurement of intellectual deterioration. This scale consists of a vocabulary test and an abstract thinking test, to be used together. Both are self-administering. The vocabulary test is comprised of forty items of the multiple choice type. Each of the items consists of a test word for which the patient must select and underscore from four words the appropriate synonym. The abstract thinking test is comprised of twenty items of the completion type. Each item requires the subject to induce a general principle and deduce a specific answer. The degree of deterioration is expressed as the conceptual quotient. It represents the ratio of the patient's abstract thinking ability to his vocabulary level. Thus, this test makes use of the fact that in mental deterioration vocabulary is relatively preserved, whereas there is a striking loss of abstract, or conceptual, thinking.<sup>17</sup>

Six of the patients with a diagnosis of schizophrenia were given the Shipley-Hartford Retreat Scale and had a median conceptual quotient of 75, indicating some intellectual impairment. However, Shipley and Burlingame<sup>16</sup> found the median conceptual quotient for 96 schizophrenic

TABLE 2—Controls and Morphine Addicts Equated for Age and Education

	Age, Yr	Education	Drug History, Yr
Controls	39.6	11.0	None
Addicts	40.6	11.0	12.7

patients in a state hospital to be 65. When the results for private and state hospital patients were combined, the median conceptual quotient was 75. These results suggest that these 6 psychotic patients with addiction to morphine were not more deteriorated than a group of schizophrenic patients who did not have the addiction.

In a further attempt to evaluate morphine as a cause of mental deterioration, the Shipley-Hartford Retreat Scale was administered to 25 nonpsychotic patients who had been addicted to use of morphine for periods varying from three to twenty years, with a mean of 12.7 years. The results were compared with those for 25 attendants at this institution. The data for these two groups were equated for age and education. The mean age, education and history of drug addicts are shown in table 2. It is noted that the two groups were comparable in age and education.

16 Shipley, W., and Burlingame, C. A Convenient Self-Administering Scale for Measuring Intellectual Impairment in Psychotics, *Am J Psychiat* **97** 1313, 1941.

17 Babcock, H. An Experiment in the Measurement of Mental Deterioration, *Arch Psychol* **18** 105, 1930. Gelb, A. and Goldstein, K. Psychologische Analysen hirnpathologischer Falle. Ueber Farbenamnesia nebst Bemerkungen uber das Wesen der amnestischen Aphasie, *Psychol Forsch* **6** 127, 1924.

Comparison of the performance of the two groups on the Shipley-Hartford Retreat Scale is shown in table 3

The ratio of the difference to the probable error of the differences (D PED)<sup>18</sup> is 1.9. This ratio must be at least 4 to insure significant superiority of one group over another. It is obvious, therefore, that the use of morphine has not increased mental deterioration, as measured by this scale in a group of addicts and compared with the results for a control group equated for age and education. Brown and Partington<sup>19</sup> found no differences between attendants and patients addicted to drugs, using a battery of tests which included the Wechsler-Bellevue test, the Ferguson form boards, the Knox cubes and the Healy Picture completion test.

The addict suffers ethical and social regression, but, as pointed out by Kolb,<sup>12</sup> this is not due to the direct effect of narcotics but, rather, is a result of social consequences of the life of addiction. In most addicts a sufficient amount of a narcotic produces a lethargy and ambition is decreased. Less attention is paid to occupation. Frequently the addict

TABLE 3—*Scores on Shipley-Hartford Retreat Scale for Controls and Addicts Expressed as the Conceptual Quotient*

	Mean	Standard Deviation
Controls	85.6	5.2
Addicts	83.6	5.7

stays away from work because of discomfort due to an insufficient amount of the narcotic or because he must look for the drugs. Many addicts associate with criminals in order to continue their supply of drugs. The need for sufficient money to maintain a "habit" frequently leads to stealing. He is held in contempt by others. He fears arrest and incarceration. All these factors lead to ethical and social regression, but intellectual deterioration in the psychologic sense has not been demonstrated.

The following case illustrates many of the pertinent observations of this study.

*Paranoid schizophrenia in a patient with drug addiction*

A white man aged 50 was the product of a congenial middle class home, of average economic, social and cultural levels. Except for an excessively close attachment to his mother, no other significant factors in his early development were elicited.

His criminal career dated from at least the age of 19, when he was arrested for petit larceny. His record since that time revealed arrests for shop lifting, automobile theft, grand larceny, robbery, vagrancy and violation of narcotic laws.

18. This measure provides a way of telling whether one group is significantly superior to another group.

19. Brown, R., and Partington, J. The Intelligence of the Narcotic Drug Addict, *J. Gen. Psychol.* 26:175, 1942.

The onset of addiction was in 1914, at the age of 20, by smoking opium, a habit which he continued until 1928, when he began to use diacetylmorphine. He later changed to morphine. Since 1914 he had abstained from drugs for only a few days at a time. Even while incarcerated he was able to obtain narcotics. He gave curiosity and associates as the reasons for first using drugs.

When admitted to this hospital, he did not show signs of physical dependence on narcotic drugs. Physical and neurologic examinations and laboratory tests revealed an essentially normal condition. He was placed in the general hospital population. Approximately eight weeks later he was admitted to the neuropsychiatric ward because of "increasing tension."

He stated that twenty years before he first began to feel the effects of machines that spoke to him about obscene sexual matters. This was ten years after the onset of addiction. This hallucination persisted for two years. It recurred ten years later and continued for several years, and recently these machines had begun to bother him again.

The patient appeared tense and suspicious. He moved his right shoulder in a manneristic fashion, explaining that his arm seemed "hazy" and was coming off. He felt electric currents going through his arm. Occasionally during interviews he stood up and said that the electricity used on him made him feel uncomfortable. He touched the area over his heart, saying that he did this because his heartstrings were broken when his mother died. He occasionally showed blocking, his speech was usually evasive, and frequently he used neologisms. He showed a high degree of tension, and when discussing his delusions he became tearful and asked that no further harm be done to him. Affect was labile and at times inappropriate.

There were elicited loosely organized delusions of persecution. He expressed the belief that the government and particularly the research department at this institution were using various machines and electricity to change his body. He said they put a moving picture machine in his stomach, and in the reflection in his eyes he was able to see the movies. He stated that they had performed an operation on him by means of the radio, they had removed parts of his body and changed its shape. He felt taller than he used to be. At times his ribs seemed hazy to him. He said that his vision had become dimmer and his palate harder. Occasionally he expressed the idea that all this was being done to remove the effects of morphine from his body. However, usually he felt that these experiences resulted from a plan to persecute him. He expressed strong guilt feelings regarding antisocial behavior, including the use of drugs. He heard people over the radio refer to incidents that had occurred to him in the past.

While awake he heard his wife and brother outside his room talking to him about his various troubles, including his present commitment, but he said he was too tired to go out and see them at the time. He was well oriented with respect to time, place and person. General information was good. Calculations were well done. There was no impairment of recent or remote memory. He had no insight.

#### COMMENT

It is noted that the patients with morphine addiction studied were not using narcotics at the time of examination. It has been observed here that the results of psychometric measurements given while the patient is still using morphine, or soon after withdrawal, are similar to the results obtained for deteriorated patients. This probably accounts for some of the published reports of deterioration in persons with

morphine addiction. Thus, the recent memory defect is temporary and quickly reversible and should not be considered intellectual deterioration, any more than an acutely alcoholic patient would be called deteriorated because of poor recent memory and difficulty in calculating. The persistent delusions and hallucinations exhibited by persons with morphine addiction are explainable on the basis of various organic and functional psychoses, to which morphine addicts, like all people, are susceptible.

An estimation of intellectual deterioration should not be made while the patient is still receiving morphine. In order to eliminate false findings, at least six weeks should elapse after withdrawal of the drug to allow for adequate recovery. One must be certain that the patient has not recently used barbiturates or alcohol. Although the use of alcohol and morphine together is relatively rare, some addicts do use large amounts of both, and the presence of alcoholic deterioration should be considered in such patients. In some cases neurosyphilis accounts for the deterioration.

#### SUMMARY

1 The incidence of psychoses (2 per cent) among incarcerated persons with morphine addiction was no higher than that (2 per cent) in a comparable group of prisoners without addiction, an observation indicating that the chronic use of morphine is not a cause of psychoses.

2 The psychoses of 19 persons with morphine addiction fell into the usual diagnostic categories. Neurologic and psychiatric examinations failed to reveal anything characteristic of a psychosis due to morphine.

3 Six schizophrenic persons with addiction to morphine were given the Shipley-Hartford Retreat Scale and were found to be no more deteriorated than a control group.

4 Twenty-five nonpsychotic patients with morphine addiction who had used morphine and other narcotics for a mean period of 12.7 years were given the same test and were not found to be deteriorated.

#### CONCLUSION

The data of this study indicate that the habitual use of morphine does not cause a chronic psychosis or an organic type of intellectual deterioration.

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# BROMINE CONTENT OF THE BLOOD IN MENTAL DISEASES

## II Manic-Depressive Psychosis

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IN A previous paper,<sup>1</sup> a survey of the literature dealing with blood bromides in mental diseases was presented. Several investigators,<sup>2</sup> have made blood bromide studies of patients with manic-depressive psychosis. Zondek and Bier,<sup>2a</sup> in 1931, reported that in 29 out of 34 cases of manic-depressive psychosis studied the blood bromine content was from 40 to 60 per cent below the normal value (1 mg per hundred cubic centimeters) established by them. These investigators obtained an average value of 0.572 mg per hundred cubic centimeters for the 34 cases but did not state whether the patients were in the manic or in the depressed stage. Sacristán and Peraita<sup>2b</sup> analyzed the blood of 13 women classified as manic, hypomanic or melancholic and obtained bromine values ranging from 0.161 to 0.684 mg per hundred cubic centimeters, with an average value of 0.423 mg. All these values were lower than the normal values obtained by the same method. Hennelly and Yates,<sup>2c</sup> using a new and more accurate analysis of their own, examined the blood of 7 male patients with manic-depressive insanity. They reported that the bromine content was low in 5 patients

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The present investigation was made possible through the courtesy of the staff of the Columbus State Hospital for the Insane, Dr J F Bateman, Superintendent. Drs Rothermich, Michael and Whittenbrook, selected the patients and furnished the diagnosis for this study.

1 Wikoff, H L, Martin, R L, and Marvin, T R. Bromine Content of the Blood in Mental Diseases. I. Dementia Precox, *Arch Neurol & Psychiat* **53** 305 (April) 1945.

2 (a) Zondek, H, and Bier, A. Brom im Blute bei manisch-depressivem Irresein, *Biochem Ztschr* **241** 491, 1931. (b) Sacristán, J M, and Peraita, M. Ueber den Bromspiegel des Blutes bei manisch-depressivem Irresein, *Klin Wchnschr* **12** 469, 1933. (c) Hennelly, T J, and Yates, E D. Blood Bromine in the Psychoses, *J Ment Sc* **81** 173, 1935. (d) Meier, C A, and Schlientz, W. Neuere Untersuchungen über den Bromspiegel im Blut bei Psychosen, *Klin Wchnschr* **15** 1845, 1936. (e) Chatagon, P, and Chatagon, C. Le métabolisme du brome dans l'organisme humain, *Compt rend Acad d sc* **202** 1119, 1936.



but stated that there was no correlation between the bromine content of the blood and the phase of the psychosis. Meier and Schlentz,<sup>2a</sup> studying the bromide content of the blood of patients with psychoses, included 10 patients with manic-depressive psychosis. Four of these patients were in the manic phase and 6 in the depressive phase. Later, when 1 of the patients previously in the manic phase entered the depressive phase, his blood bromides were redetermined. These authors stated that the blood bromides were low in patients with manic-depressive psychosis, an observation confirmed in all but 2 of their cases. Pierre and Camille Chatagon<sup>2b</sup> found that the blood bromine values were higher than normal in 23 out of 31 cases of manic-depressive psychosis which they had studied.

Because the results obtained by previous investigators were not in agreement, and because the total number of cases reported by any of these workers was relatively small, an extensive study of the blood bromide content of patients with manic-depressive psychosis was made.

The subjects chosen had all been inmates of the Columbus State Hospital for the Insane for more than three months, and some had been in residence there for more than ten years.

The method of bromide analysis previously devised by one of us (H. L. W.)<sup>3</sup> was used for this investigation. The accompanying table gives the results for 116 patients with manic-depressive psychosis. In 5 instances the same patients were reexamined at a later date. Eighty-three (68.6 per cent) of the determinations were made while the patients were in the stage of remission, 27 (20.3 per cent), while in the manic stage, and 11 (9.1 per cent), while in the depressive stage.

Since in the majority of the patients the condition was in a stage of remission when samples of blood were drawn, the general average for bromine (0.459 mg. per hundred cubic centimeters of whole blood) for all the patients was greatly influenced by this group. Sixty of the 83 subjects in the remission stage (72.4 per cent) had less than 0.459 mg. of bromine per hundred cubic centimeters of whole blood, while only 70 of the entire series of 116 subjects, or 60.3 per cent (72 of 121 determinations, or 59.5 per cent), had less than the average amount (0.459 mg.). Although the bromine content for all subjects ranged from 0.08 to 2.66 mg. per hundred cubic centimeters of blood, actually there were only 7 whose bromine value exceeded 1 mg. per hundred cubic centimeters.

The 83 subjects in the remission stage had an average of 0.349 mg. of bromine per hundred cubic centimeters of blood, with 50 (60.5 per cent) of them having less than the average amount of bromine. The individual amounts ranged from 0.08 to 0.90 mg. per hundred cubic centimeters.

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3 Wikoff, H. L., Bame, E., and Brandt, M. A Method for the Determination of Bromide in a Protein-Free Filtrate, *J. Lab. & Clin. Med.* **24**: 427, 1939.

The limited number of patients in the manic and in the depressive stage does not seem to warrant conclusions for these groups at this time. However, it may be noted that the average bromine values for the patients in these two groups, 0.728 and 0.629 mg, respectively, were lower than the average value (0.81 mg of bromine per hundred

*Bromine Content of Blood of Patients with Manic-Depressive Psychoses*

Remission Stage						Manic Stage			Depressive Stage		
Bromine, Mg /100 Cc Whole Blood			Bromine, Mg /100 Cc Whole Blood			Bromine, Mg /100 Cc Whole Blood			Bromine, Mg /100 Cc Whole Blood		
Case No	Age		Case No	Age		Case No	Age		Case No	Age	
Males			Females			Males			Males		
1	59	0.32	44	54	0.18	84	68	0.40	108	48	0.92
2	55	0.57	45	60	0.40	85	72	0.50	109	60	0.45
3	72	0.48	46	88	0.14	86	51	0.47	110	57	0.80
4	60	0.50	47	73	0.13	15*	46	0.49	111	58	0.34
5	68	0.36	48	71	0.12	87	55	0.55	23*	40	0.36
6	65	0.32	49	55	0.16	88	60	0.60	112	69	0.64
7		0.40	50	55	0.15	89	41	0.75			
8	46	0.00	51	66	0.20	89*	45	0.64	Females		
9	63	0.73	52	56	0.11	90	68	2.66	113	72	0.94
10	66	0.67	53	53	0.19	(restrained)			114	42	0.76
11	63	0.34	54	40	0.32	90*	69	0.54 (not restrained)	115	58	0.94
12	47	0.45	55	52	0.48				102*	38	0.22
13	54	0.35	56	60	0.67	91	68	0.71	116	46	0.55
14	67	0.41	57	38	0.13	92	54	0.50			
15*	45	0.67	58	52	0.27	93	63	0.13			
16	69	0.23	59	70	0.38	Females					
17	56	0.21	60	42	0.34						
18	73	0.49	61	64	0.17	94	68	0.50			
19	81	0.22	62	54	0.31	95	68	0.98			
20	71	0.62	63	61	0.41	96	61	0.38			
21	36	0.49	64	62	0.25	97	77	0.77			
22	55	0.10	65	56	0.17	98	40	0.32			
23*	41	0.77	66	40	0.08	99	47	0.42			
24		0.27	67	55	0.19	100	52	0.94			
25	48	0.59	68	47	0.32	101	53	1.11			
26	68	0.20	69	52	0.36	102*	38	1.34			
27	68	0.59	70	46	0.30	103	59	0.45			
28	68	0.13	71	41	0.17	104	35	0.41			
29	49	0.52	72	57	0.39	105	48	1.90			
30	57	0.80	73	45	0.28	106	58	0.81			
31	32	0.50	74	57	0.13	107	57	0.89			
32	63	0.37	75	52	0.25						
33	37	0.67	76		0.21						
34	40	0.78	77	57	0.24						
35	55	0.62	78	32	0.17						
36	54	0.59	79	56	0.19						
37	55	0.29	80	53	0.09						
38	65	0.40	81	48	0.23						
39		0.12	82	46	0.32						
40	61	0.18	83	54	0.15						
41	41	0.33									
42	67	1.13									
43	76	0.50									

\* The asterisk indicates that two determinations were made

cubic centimeters of blood) previously determined<sup>4</sup> for normal healthy persons residing in Columbus. Eighty per cent of the blood bromine values for the normal subjects differed from the average value by less than 0.2 mg per hundred cubic centimeters, but only 50.8 per cent of the values for the manic-depressive group were within 0.02

<sup>4</sup> Wikoff, H. L., Brunner, R. A., and Allison, H. W. The Normal Bromine Content of the Blood of Healthy Individuals, *Am J Clin Path* **10** 234, 1940

mg of the average value. While the subjects with dementia precox previously studied<sup>1</sup> also had less bromine in the blood than the normal persons, 80 per cent of them had blood bromine values differing from the average amount by less than 0.02 mg per hundred cubic centimeters.

#### SUMMARY

Of the 116 patients in this series, 83 were in the stage of remission. The average bromine content of the blood of these 83 patients was found to be 0.349 mg per hundred cubic centimeters. This value is considerably lower than the average (0.81 mg per hundred cubic centimeters of blood) obtained by the same method for normal persons residing in the same city.

Twenty-seven patients in the manic stage had an average blood bromine content of 0.728 mg per hundred cubic centimeters. Eleven patients in the depressive stage had an average blood bromine content of 0.629 mg per hundred cubic centimeters.

For both the manic and the depressive patients, the average value for blood bromine was appreciably higher than the average for patients in the remission stage. However, the average for each group, in manic and depressive stages and in remission, is below that for normal persons living in the same city.

In only 10 of the entire series of 116 patients was the amount of bromine in the blood above the average found for normal persons.

Ohio State University College of Medicine

# CEREBRAL DYSRHYTHMIA AND PSYCHOPATHIC PERSONALITIES

A Study of Ninety-Six Consecutive Cases in a Military Hospital

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MEDICAL CORPS, ARMY OF THE UNITED STATES

RECENT communications report a high proportion of electroencephalographic abnormalities among persons with behavior disorders (Hill and Watterson,<sup>1</sup> Silverman,<sup>2</sup> Knott and Gottlieb<sup>3</sup> and Silverman and Rosanoff<sup>4</sup>) Their findings suggest that organic factors should be weighed more heavily in considering the etiology of psychopathic states

The chief psychiatric connotations of psychopathy are widely understood Cleckley,<sup>5</sup> Darling<sup>6</sup> and others have suggested that the condition arises from a defective development of the superego, and constitutional factors have been emphasized by Henderson<sup>7</sup> and others For our purpose, it appeared unwise to deviate from the view that the diagnosis "constitutional psychopathic state" should be made only when the longitudinal study of the patient's personality presents sufficient evidence for the formulation of a valid psychodynamic interpretation of that entity However, partial manifestations of the psychopathic character, often considered as identical with the condition per se, may occur in

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From the Neuropsychiatric Service, Mason General Hospital, Brentwood, N Y

1 Hill, D, and Watterson, D Electroencephalographic Studies of Psychopathic Personalities, *J Neurol & Psychiat* **5** 47-65, 1942

2 Silverman, D Clinical and Electroencephalographic Studies on Criminal Psychopaths, *Arch Neurol & Psychiat* **50** 18-33 (July) 1943

3 Knott, J R, and Gottlieb, J S Electroencephalographic Evaluation of Psychopathic Personality, *Arch Neurol & Psychiat* **52** 515-519 (Dec) 1944, Electroencephalograms in Psychopathic Personalities, *Psychosom Med* **5** 139-141, 1943

4 Silverman, D, and Rosanoff, W R Electroencephalographic and Neurologic Studies of Homosexuals, *J Nerv & Ment Dis* **101** 311-321, 1945

5 Cleckley, H The Mask of Sanity, St Louis, C V Mosby Company, 1941

6 Darling, H F Definition of Psychopathic Personality, *J Nerv & Ment Dis* **101** 121-126, 1945

7 Henderson, D K Psychopathic States, New York, W W Norton & Company, Inc, 1939

post-traumatic conditions or as sequelae of encephalitis, or they may accompany the progressive disorganization of activity of the frontal lobes due to cerebral tumor. Congenital syphilis, complications of pertussis referable to the central nervous system and other disturbances having their origin in infancy may also play a role in its development, and certain disorders in which episodic aggressive activity is a salient feature are thought to be allied to the epileptic states (Henderson<sup>7</sup>). While it cannot be presumed that every case of such a disorder will be eliminated from the constitutional psychopathic group on the basis of the psychiatric formulation, the etiology of the organic variants becomes clear when a cleavage from the pattern of a hitherto normal personality occurs as an aftermath of a neurologic condition.

By electroencephalographic recording there is hope of identifying certain cases in which, though the neurologic evidence of involvement may be obscure, the organic contribution to the causation of psychopathy may be large. However, it is known that abnormal records do occur in normal control groups, and in the absence of specific criteria of abnormality, such as the records of paroxysmal activity (Gibbs<sup>8</sup>) offer in cases of epilepsy, judgment concerning the clinical significance of an abnormal electroencephalographic record in the diagnosis of a psychopathic disorder must have its basis in statistical comparisons.

The incidence of so-called electroencephalographic abnormalities in normal population groups has varied from 5 to 20 per cent in different studies. Such differences may be explained by variations in the rigidity with which the biologic criteria of normality are applied and the vagaries in classification of records, which may cause certain borderline findings to be interpreted as normal in one series and as abnormal in another. Particularly in the interpretation of records containing slow sequences, the amplitude of the slow waves may be the deciding factor in placing a record in a normal or in an abnormal category.

The occurrence of high percentages of electroencephalographic abnormalities in series of psychopathic subjects already reported in the literature dictates the need for further studies of groups selected in different situations. Our study was undertaken to provide data concerning the incidence of electroencephalographic abnormalities in persons with constitutional psychopathic states diagnosed in a military hospital. In a large series of these patients the severer manifestations are the rule, since milder personality maladjustments are usually studied in outpatient clinics, also, the diversity of symptoms is sufficient to make the group representative of the total concept of psychopathy postulated by numerous investigators.

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8 Gibbs, F. A. *Electro-encephalography*, in Solomon, H. C., and Yakovlev, P. I. *Manual of Military Neuropsychiatry*, Philadelphia, W. B. Saunders Company, 1944.

Every effort was made to secure a nonselected group and to achieve accurate diagnostic consideration in each case. The patients were taken in consecutive order for electroencephalographic study after they had appeared before a formal hospital board of three experienced psychiatrists, all section chiefs in a specialized military neuropsychiatric hospital. Complete medical, neurologic, laboratory and, where indicated, roentgenologic studies were made to rule out coexisting organic disease before the patients were brought before the board. Various lengths of service were represented in the group, enlisted women as well as men were included, and a variety of manifestations of psychopathy in different degrees of severity were represented. When it was evident that a suitably extensive trial at duty had not been given to assure opportunity to adjust, the patient was returned to duty with recommendation for further trial. The series included 96 patients. Clinical data were also available on 8 other patients who appeared before the hospital boards during the period in which the study was being conducted.

#### PSYCHIATRIC EVALUATION OF CASE MATERIAL

In all cases included the diagnosis of constitutional psychopathic state was made in accordance with the military terminology during the period selected for the survey. In the case study, the severity of each of a variety of manifestations of psychopathy was assessed for the purpose of establishing correlations between the gravity of the symptoms and the type of electroencephalographic record. The manifestations included in this survey were inadequacy, emotional instability, aggression, overt asocial behavior in the premilitary and in the military situations, absence without leave, alcoholism, drug addiction, sexual psychopathy and fabrication. The coexistence of psychosomatic complaints and of organic illness was also considered. There were 96 men and 8 women. The ages ranged from 18 to 42 years. Approximately 45 per cent of the total series were between the ages of 21 and 26 years. Total durations of service varied from five months to four and one-half years, and there was an approximately even distribution of subjects with periods of service between twelve and thirty-six months. Twelve of the men were military prisoners at the time of admission to the hospital. A brief summary of the salient psychiatric data follows.

*Inadequacy*—Mild manifestations were defined to include marginal social and economic adjustment in premilitary life, lesser degrees of nomadism, frequent lack of or change in employment, and truancy and other behavior difficulties during childhood. In the intermediate grade of inadequacy, in addition to some or all of the aforementioned manifestations, were repeated minor infractions of the law, marital difficulties and definite evidence of military maladjustment. The severest form

of inadequacy was characterized by petty thievery of frequent occurrence, conviction for criminal offenses or serious military insubordination. Approximately 25 per cent of the total number of patients showed severe inadequacy, and 6 of the 12 military prisoners were in this group. Another 50 per cent of the total series gave evidence of inadequacy of intermediate severity. There appeared to be a high correlation between the severity of manifestations of inadequacy in premilitary life and the frequency of absences without leave that occurred during military service.

*Emotional Instability*—Twenty-five per cent of the patients had a history of one or more suicidal attempts in response to frustration or as an effort to relieve a situation regarded as intolerable. These personalities were assessed as displaying emotional instability of the severest degree, as were 2 others with a history of self mutilation. One of the latter admitted intent to avoid hazardous duty. A history of mood depressions with the existence of manifestations of lesser severity was the basis for assessing instability of intermediate severity, and 30 per cent of the total number belonged in this category. The rest had manifestations of lesser severity.

*Aggression*—Twenty per cent of the total series did not manifest aggressive tendencies, an additional 40 per cent showed aggression as a subdominant characteristic. Overt hostility, frequent fights and marital quarrelsomeness of marked degree were manifested by 35 per cent. One member of the series showed episodic uncontrolled aggression, homicidal in character, and 4 others manifested it to a degree that could be considered either as homicidal in intent or as necessitating criminal action.

*Overt Asocial Behavior*—Seventy per cent of the series gave no concrete evidence of overt asocial behavior during the premilitary period. Of the remainder, 9 had a substantiated history of one or more arrests or confinements of minor character, and 10 had at least one reformatory or prison sentence in the premilitary record with additional evidence of criminal tendencies. There were no confirmed criminals in the group. In evaluating the military evidence, only military records substantiating the occurrence of thievery or other asocial trends were considered, and absence without leave and minor evidences of insubordination of debatable value in indicating criminal tendencies were eliminated. Sixteen per cent had one military conviction, and the offenses of 2 others were graded as more serious, for the offense was a repetition of one for which a conviction had been secured previously in civilian life.

*Absence Without Leave*—Forty-six per cent of the men had no significant history of such absences, and none of the women had committed the offense. A small percentage of the men had fewer than

four offenses, and approximately 40 per cent had four or more. The remaining 10 per cent had had one or more absences of such long duration as to indicate that the offense represented the severest manifestation in this regard.

*Alcoholism*—One third of the total number showed some evidence of alcoholism, and of these, 20 had been described in prior clinical records as "chronically alcoholic." These 20 subjects gave abundant civilian and military evidence of the use of alcohol, the other alcoholic patients had lesser manifestations. None of our subjects gave evidence of the performance of definitely asocial acts while under the influence of alcohol.

*Addiction to Drugs*—This was not a common finding in the present series. Seven patients indicated that they smoked marihuana cigarettes, another 7 gave a history of having at one time or another experimented with the use of more conclusively habit-forming drugs.

*Sexual Psychopathy*—Twelve of the men gave a history of sexual psychopathy, but only 2 could be regarded as overtly homosexual. The remainder had controlled their homosexuality, participating intermittently either because of lack of heterosexual outlets or for financial gain. One exhibited perversion in heterosexual relationships.

*Medical History*—Evidence of organic disease as a cause of admission to the hospital played an unimportant role in this series. Seven men were admitted to the hospital for psychosomatic complaints, however, and an additional 8 patients, who were admitted because of consistent failure to adjust to the military situation, complained of psychosomatic symptoms after admission. Five patients had a history of head injury, but no neurologic sequelae were present. In no case did encephalitis or any manifestation of childhood disease that might be expected to cause the development of psychopathic character appear to be a contributory factor.

#### ELECTROENCEPHALOGRAPHIC RESULTS

A standard eight lead electroencephalographic record, recommended by the Office of the Surgeon General, United States Army, and its electroencephalographic consultant, Dr F. A. Gibbs, was taken in each case. Studies were repeated when the initial recording did not provide satisfactory results. Eight of the total series of 104 recordings were eliminated from consideration because artefacts made the results unsatisfactory. Recording was usually done at an amplification of 8 mm per 50 microvolts. Care was taken not to filter the faster frequencies excessively, so that this type of activity would not be eliminated from the records. A twenty minute record, including combinations of all leads and two minutes each of hyperventilation and posthyperventilation, was routinely used.

With qualifications to be specified, the Gibbs<sup>8</sup> criteria for classification of records were followed. All records containing  $8\frac{1}{2}$  to 12 per second frequency and those showing low voltage activity were classified in a single "normal" group.



Particular care was taken in classifying the records with borderline slow (S-1) activity, the following statement by Gibbs being taken as the basis for distinguishing between the S-1 and the  $8\frac{1}{2}$  to 9 per second frequencies "Moderate amount of activity slower than  $8\frac{1}{2}$  per second in any lead. Amount is considered in terms of amplitude and frequency of the slow activity, percentage of time present, and the number of leads in which it appears" We arbitrarily established 35 microvolts as the criterion of amplitude for slow sequences in this study, and slow activity of lesser amplitude was consistently interpreted as low voltage. Also by arbitrary definition we classified records showing the F-1 and S-1 frequencies of the Gibbs classification as borderline abnormal and the records with the F-2, S-2 and paroxysmal activities as abnormal. The term paroxysmal activity was more broadly interpreted than is the usual practice under the Gibbs classification and was made to include slow dysrhythmias of paroxysmal character. These were mentioned by Jasper<sup>9</sup> (Penfield and Erickson, page 403).

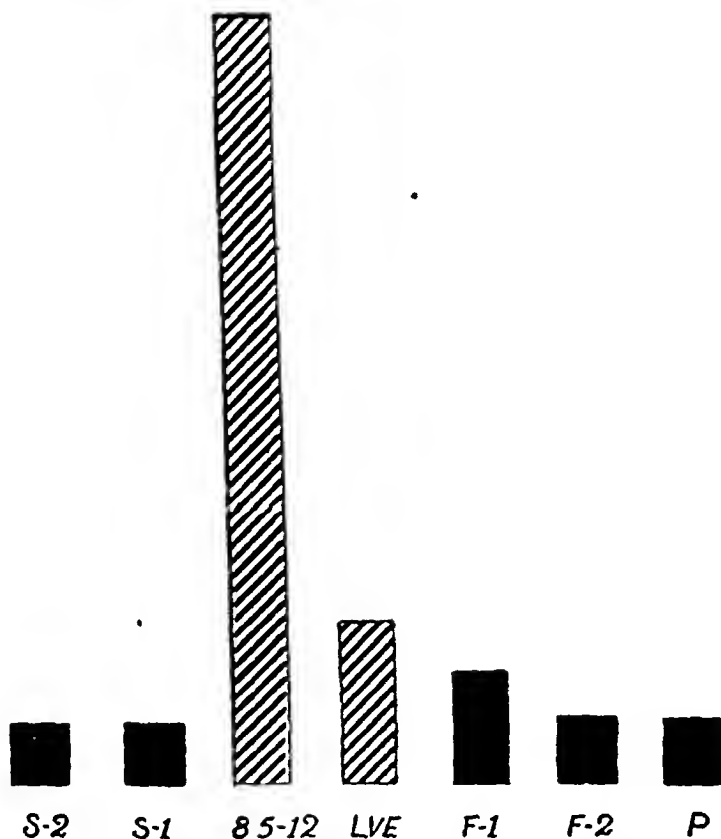
Of the 96 records, 72 per cent fell within the normal range (figure). This included all the records of  $8\frac{1}{2}$  to 12 per second frequency and of low voltage activity. The 61 per cent of the total which constituted the records of  $8\frac{1}{2}$  to 12 per cent frequency was made up of 32.6 per cent which were quite regular in amplitude and frequency, 13.7 per cent showing mild irregularity of amplitude and 14.7 per cent showing mild irregularity of frequency. Records of borderline abnormality, the S-1 and F-1 categories, comprised 12.6 per cent of the total. This included 4.2 per cent with S-1 activity and 8.4 per cent of F-1 activity. The percentage of records of the S-1 type would have been increased had several of the records with paroxysmal sequences of slow activity been classified in the S-1 category rather in the category of paroxysmal activity. Abnormal records of the F-2 and S-2 type made up 9.4 per cent of the total of our series, 4.2 per cent were of the S-2 variety, as compared with 0.7 per cent in Gibbs's control series, and 5.2 per cent were of the F-2 type, as compared with 0.4 per cent of Gibbs's controls. Abnormal records with paroxysmal activity represented 5.2 per cent of our total series, but, as previously indicated, this figure included "paroxysmal slow dysrhythmias" and therefore could not be compared reliably with Gibbs's controls. Five records showed some degree of build-up on hyperventilation. Two of these were classified with the normal records because the build-up was not significant and the records were not otherwise abnormal. For other reasons, 2 other records with build-up were classified as in the paroxysmal and 1 in the F-2 category.

The records were also studied with a view to determining whether or not an increased incidence of abnormality in the electroencephalograms was associated with the various manifestations of psychopathy of the severest degree. Certainly, there was no tangible evidence that

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<sup>9</sup> Jasper, H. H. *Electroencephalography*, in Penfield, W., and Erickson, T. C. *Epilepsy and Cerebral Localization*, Springfield, Ill., Charles C. Thomas, Publisher, 1941.

this was the case. Of 25 patients rated as presenting the severest manifestations of inadequacy, 5 showed abnormal records, 3 of these being of the F-2 and 1 of the paroxysmal type. In addition, 2 of this group had records of borderline (F-1) type. Of 37 patients manifesting less severe grades of inadequacy, 2 had records of paroxysmal activity, and 2 records of F-2 type. The 23 patients who showed the severest emotional instability included 3 who had abnormal records (2 with the F-2 type and 1 with the paroxysmal type) and 3 who had borderline abnormal (F-1) records. Of 44 subjects manifesting the



Histogram indicating the distribution of electroencephalographic frequencies for 96 records in terms of the Gibbs classification. Slow dysrhythmias of paroxysmal character are included with the paroxysmal type. Diagonal lines indicate the distribution of records conventionally designated as normal, black indicates the distribution usually regarded as abnormal. All records were obtained from patients with disorders diagnosed as a constitutional psychopathic state.

Analysis of the record showed that 72.5 per cent fell in the normal range (61 per cent in the 8½ to 12 per second category and 11.5 per cent in the low voltage category), 12.6 per cent were borderline abnormal (4.2 per cent in the S-1 category and 8.4 per cent in the F-1 category), 14.6 per cent were abnormal (4.2 per cent in the S-2 category, 5.2 per cent in the F-2 category and 5.2 per cent in the paroxysmal category) and 5.2 per cent showed a build-up response on hyperventilation.

lesser degrees of emotional instability, 4 had abnormal records, including 3 with the paroxysmal and 1 with the S-2 type. With respect to manifestations of aggression, overt asocial behavior, absence without leave, alcoholism, drug addiction and homosexuality, there was no difference

in the incidence of abnormality between patients with negative and those with positive histories. In the group of 12 prisoners, 2 had records with paroxysmal activity, and 2 had records of the F-2 type, however, the number of prisoners was too small to render the apparently larger incidence of abnormality significant as compared with that for the non-prisoner group.

The over-all survey of our material shows a somewhat higher incidence of electroencephalographic abnormality in this series of 96 patients with psychopathic states diagnosed in the military setting than in normal controls reported in the literature. However, our percentage of abnormality is low as compared with that for other recently reported series of psychopathic subjects. In small part, this may be due to rigid criteria employed in designating a record as abnormal, a conservatism which we believe to be justifiable in view of the present lack of electrophysiologic standards for assessing the variations of the normal. Otherwise this series of subjects selected by psychiatric criteria as constitutionally psychopathic is not notably set apart from normal standards by electroencephalographic abnormality. Whereas specific exception can be made to this interpretation so far as the relatively higher incidence of records containing S-2, F-2 and paroxysmal activity is concerned (as compared with the over-all incidence of abnormality), it is our view that further extension of knowledge in the field of electronic recording may lead eventually to the elimination of subjects presenting such records from the category of the constitutional psychopathic state.

#### COMMENT

Whereas the present study of persons with a disorder diagnosed as constitutional psychopathic state in the military setting shows a somewhat higher incidence of abnormal records than would be expected in a corresponding group of normal controls, it was not sufficiently high to indicate that the usual psychiatric criteria carefully applied are ineffective in screening out the cases with strong organic determinants. The diagnostic criteria used in the selection of subjects were based on the evaluation of the total personality, indicating in the longitudinal history of the patient a continuous projection of hostility onto the environment. Search of the history for manifestations of the symptoms most frequently associated with psychopathy was regarded as the marshaling of evidence to support the diagnosis in a particular case. The well known fact that some, even all, of these symptoms might develop as an aftermath of infection of the central nervous system or of trauma, and that undisputed infantile or adolescent involvement may appear to influence the subsequent development of psychopathic character, leads us to recommend, however, that those patients who show definite

electroencephalographic abnormality be reexamined with a view to excluding a possible organic cause

It might be expected that a correlation between the symptoms of psychopathy and electroencephalographic abnormality would become apparent in a higher incidence of abnormal records for persons showing severe as compared with mild manifestations. A series of manifestations, including inadequacy, emotional instability, aggression, homosexuality, alcoholism and absence without leave, were evaluated throughout our series and graded in order of severity. There appeared to be no obvious relation between severity and degree of record abnormality.

#### SUMMARY

Electroencephalographic tracings were obtained from 96 of a series of 104 patients with a disorder diagnosed as constitutional psychopathic state in a military setting. Within the special situation from which the patients were obtained, the sample was unselected. The personalities were evaluated first by psychiatric criteria, so that the finding of electroencephalographic abnormality did not influence diagnostic judgment. The records were classified in accordance with the Gibbs criteria with the single exception that records showing certain slow dysrhythmias of paroxysmal character were classified with records of paroxysmal activity rather than with those containing slow sequences. The percentage of abnormal records did not greatly exceed the reported incidence of abnormality in normal control groups studied by different investigators, although we did obtain a definitely higher percentage of records with F-2 and S-2 frequencies than has been obtained for normal controls. We find no relationship between the severity of different manifestations of psychopathy and the incidence of abnormality in records.

## FLEXIBLE ELECTRODE-CARRYING HEADGEAR FOR ELECTROENCEPHALOGRAPHIC EXAMINATION

A R McINTYRE, M D  
AND  
A L DUNN, M A  
OMAHA

THERE are several advantages to be gained by the employment of a mechanical device for carrying the electrodes used in making contact with the scalp in electroencephalographic examinations. Any method using gauze or other types of bands to hold the electrodes in place is uncertain and unwieldy. The technic which utilizes collodion or similar cementing material to fasten the electrodes is somewhat slow and for best results requires a skilled operator to apply and to remove the electrodes. There is a need for a means of shifting pairs or groups of electrodes rapidly to any part of the skull, as in delineating a tumor. In the interests of obtaining maximum cooperation from the patient, especially with children, the time of examination should be kept to a minimum when possible and the necessary record obtained rapidly.

With these considerations in mind, work was undertaken to develop a mechanical device which would aid in solving these problems. Particular attention was focused on designing an electrode and a means for mounting it which would be sufficiently flexible, several methods were tried and discarded in favor of the system finally decided on.

### DETAILS OF CONSTRUCTION

The oval band is constructed of  $\frac{1}{8}$  inch (32 mm) fiber, having such dimensions as to allow approximately 2 to 3 inches (5 to 7.5 cm) clearance all around when placed over a man's head of average size (fig 1). On this oval band are mounted two fiber straps carrying two electrodes each and so shaped as to maintain 2 to 3 inches clearance around the scalp. The electrodes carried on these straps are intended primarily to make contact with the frontal and parietal areas in a routine examination (fig 2) but are arranged so flexibly that any portion of the scalp from the occipital to the frontal region can be reached.

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This work was aided in part by a grant from the Johnson and Johnson Foundation.

From the Department of Physiology and Pharmacology, University of Nebraska College of Medicine.

effectively Owing to the special construction of the electrode system, several electrodes may be mounted on any of the bands for exploring particular areas of the scalp

The entire assembly can be clamped to a cot by means of a bracket which embodies a padded neck rest adjustable for height (fig 3) A hinge (with a locking device) is provided in this bracket, which makes

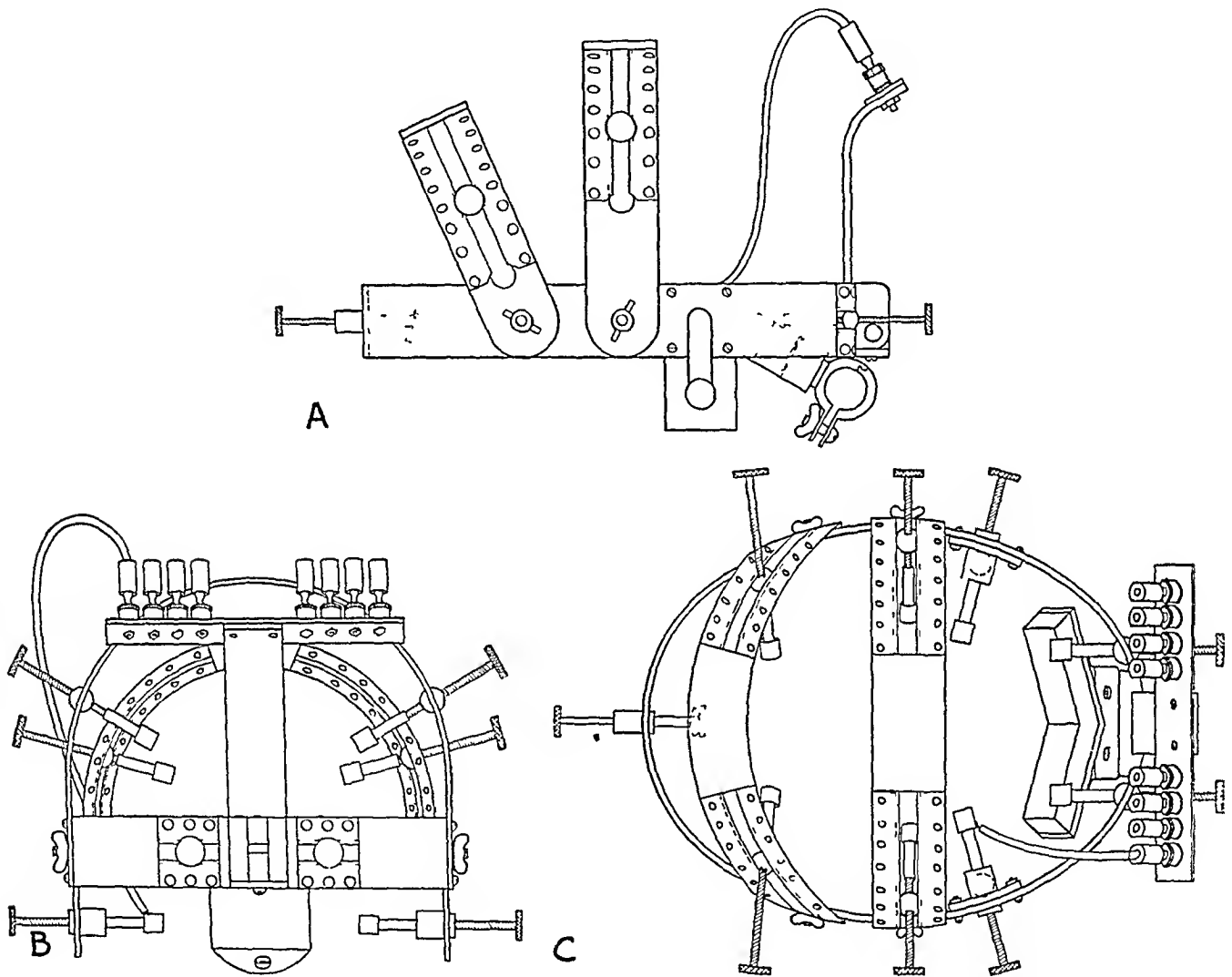


Fig 1—Diagrams showing three views of the electrode-carrying headgear

it possible to swing the headgear over the patient's head quickly and easily The assembly is held in alinement with the patient's head by means of a padded spring tension nose piece, which bears lightly but firmly on the bridge of the nose and the forehead Maintenance of the headgear in position is also aided by the mastoid electrodes The bracket which clamps the headgear to the cot carries all the weight of the device, none of it being allowed to bear on the patient's head

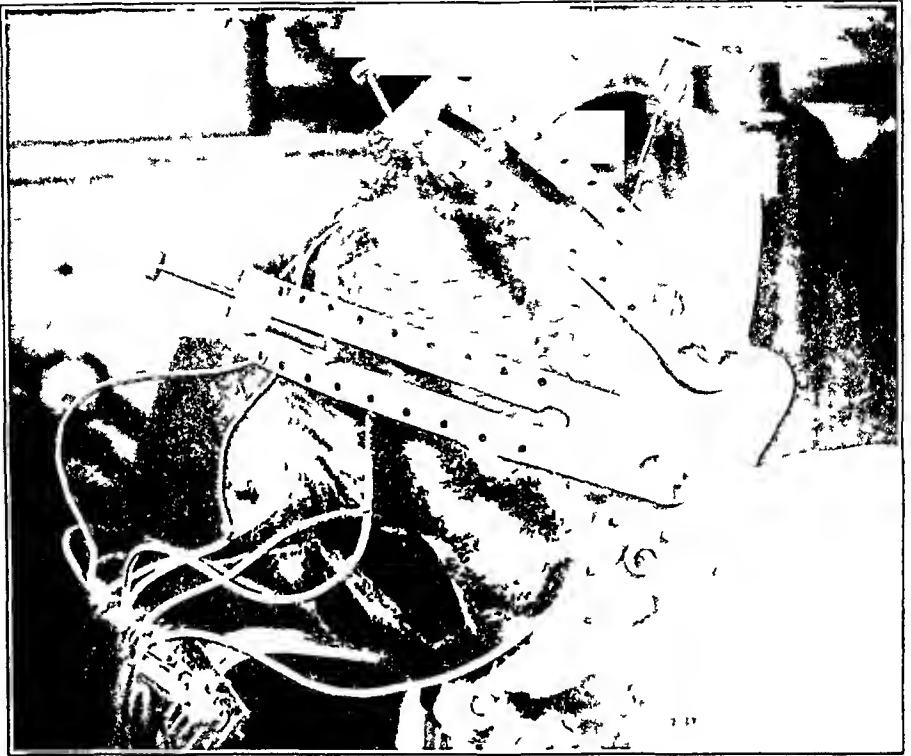


Fig 2—Electrode-carrying headgear in place for recording

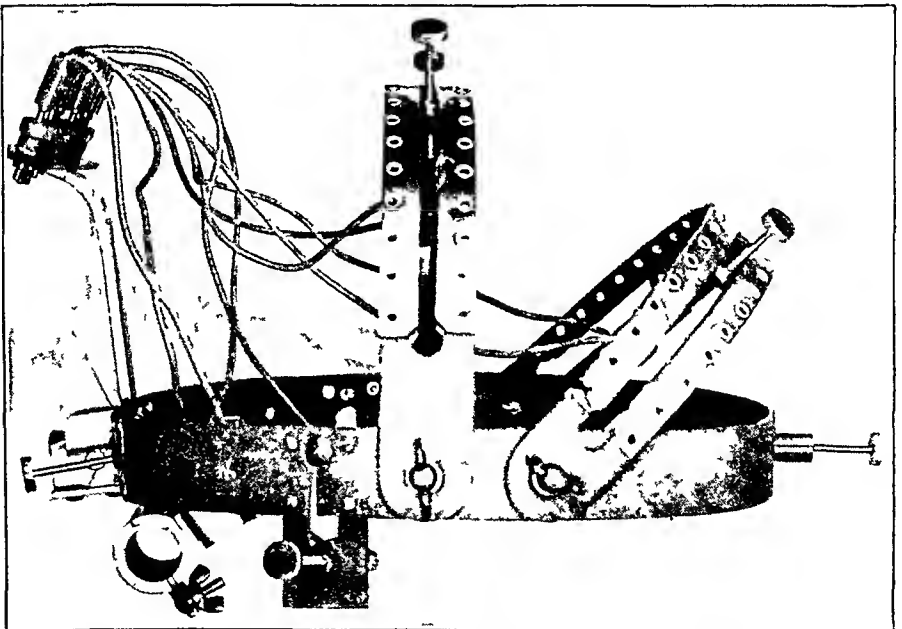


Fig 3—General view showing adjustable clamp for cot

## ELECTRODE DETAIL

The frontal, parietal and occipital electrodes are constructed similarly (fig 4). A contact cup (*A*) is arranged to swivel on the end of the shaft (*C*) and is provided with light tension by a spring (*B*). This

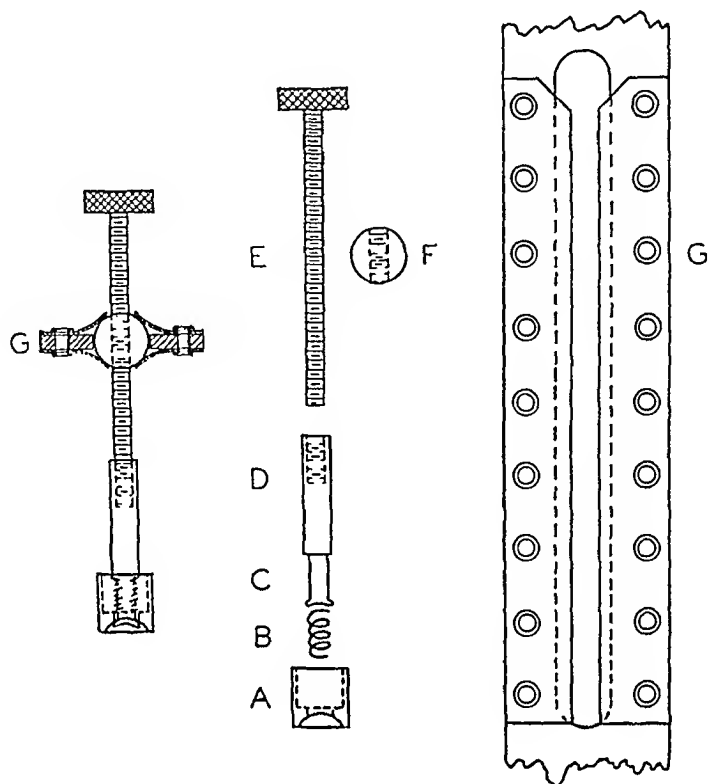


Fig 4—Diagrams showing details of electrodes

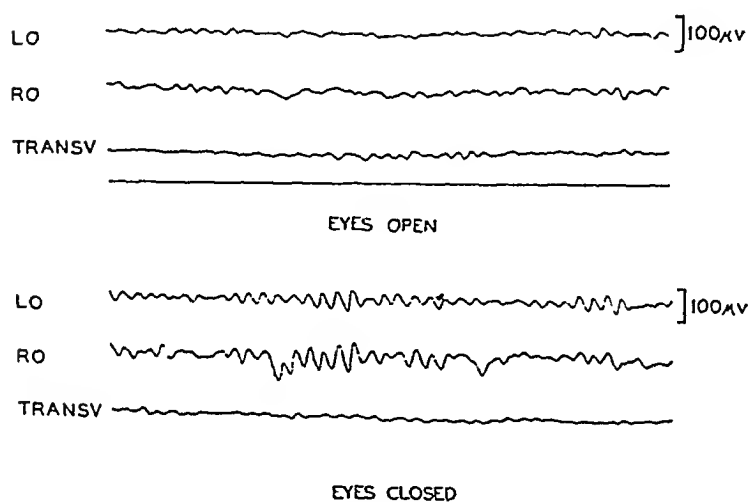


Fig 5—Sample record obtained with the headgear

allows for automatic conformation to the scalp. An insulating link (*D*) of polystyrene or other similar material is interposed, and this entire device is carried on a threaded adjusting rod (*E*), which passes through a



threaded ball (*F*) This ball works in a slide (*G*) built into the adjustable bands of the headgear Slots equal in width to the diameter of the ball are cut in the bands, and brass-guiding strips are eyeleted to the straps to give a sliding arrangement An opening is provided at the end of each slide to allow for introduction of additional electrodes

The mastoid electrodes differ only in having the ball (*F*) contained in a conventional socket, which may be moved in a slot in a fiber piece extending below the oval section

All metal parts are finished in nickel plate The connections from the electrodes are brought up to a terminal board, whence they proceed to the electroencephalograph Electrode jelly is used to facilitate contact between the electrodes and the scalp A sample of a record obtained with the headgear is shown in figure 5

#### SUMMARY

A flexible electrode assembly for use in electroencephalographic examination has been developed

A rapid means of applying and removing the electrodes is provided

The special construction of the electrodes allows great flexibility in routine examination or in exploring specific areas of the scalp, as in delineating tumors of the brain

The time for the examination has been reduced to a minimum for both patient and operator

University of Nebraska College of Medicine

## A CLIP-ON ELECTRODE FOR USE IN ELECTROENCEPHALOGRAPHY

DOROTHY L. NIXON

NEW HAVEN, CONN

IT IS assumed that most electroencephalographic laboratories employ a more or less standard type of electrode, viz., a flattened solder pellet, which is attached to the scalp with collodion.

For several years my associates and I have utilized a convenient clip-on electrode which was adapted from a somewhat similar type of electrode, as described by Darrow<sup>1</sup> in 1940. This clip-on type of electrode eliminates the application of collodion, thereby accelerating the procedure of applying electrodes. It is simply and securely attached to the scalp without discomfort to the patient. This method can be applied only when the patient has a sufficient amount of hair.

Simultaneous recordings made with solder pellet and clip-on electrodes were found to be identical.

### CONSTRUCTION AND APPLICATION OF THE CLIP-ON ELECTRODE

A rust-resistant metal is preferred if it is available, but we have found that any semipliable metal can be used. As an item of convenience, we have found that ether cans afford satisfactory results.

Two flat pieces of metal are cut, one approximately 2 by 1 cm and another approximately 2.5 by 0.5 cm. These strips of metal may be cut either slightly larger or slightly smaller, but the given dimensions will make an average-sized electrode. The wider piece is bent lengthwise, just enough space being allowed to insert the smaller piece, or the electrode "lever" (fig. 1 *A*). After the lever is inserted, the lower corner of the electrode is cut off to permit freedom of the lever when in motion, and the corners of the projecting lever edge are cut off or filed down to facilitate handling (fig. 1 *B*). Next, a hole is punched entirely through the layers of metal, approximately 2 mm from the top of the electrode and above the clipped under edge. A piece of sturdy wire is then inserted through the perforation and soldered to each side of the electrode to hold it firmly in place. This device is then mounted and soldered to the outer surface of a cup to form the base of the electrode.

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From the Laboratory of Electroencephalography, Department of Psychiatry and Mental Hygiene, Yale University School of Medicine.

1 Darrow, C. W. Convenient Electroencephalographic Electrode, *Proc Soc Exper Biol & Med* **45** 301-302 (Oct) 1940.

(fig 1 C) The cup is merely a no 3 round head brass paper fastener of which the stem has been removed and the rounded under edge has been filed off to permit thorough cleansing after use (We utilize this cup type of electrode, applied with collodion, when there is not a sufficient amount of hair to apply the clip-on type of electrode) One end of the usual electrode wire is then soldered to the outer surface of

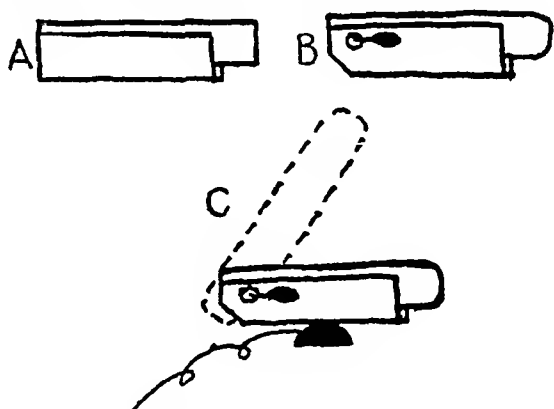


Fig 1—Diagrams showing construction of the clip-on electrode

the cup, and the electrode is ready for use Photographs of the clip-on electrode as seen from three different angles are shown in figure 2

To apply the clip-on electrode, the cup is filled with electrode paste The hair is separated in the usual manner, the scalp is rubbed well with electrode paste, and the electrode is placed on the exposed scalp With

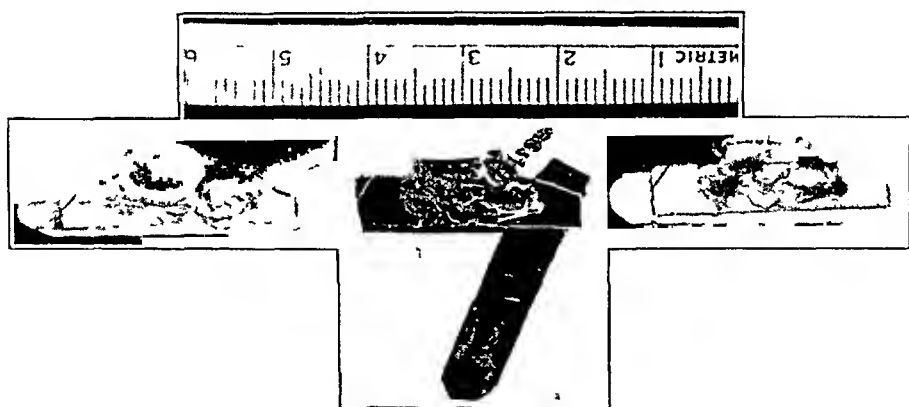


Fig 2—Three views of the clip-on electrode

the lever in an upright position, a few strands of hair are drawn from either side and across the electrode, and the lever is gently pushed to a closed position over the strands of hair

An electrode of this type will last indefinitely if it is thoroughly cleansed, preferably with acetone, after each application If the electrode is not properly cleansed, it is likely to deteriorate quickly A film is

apt to form on the inner surface of the cup, which may cause artefacts, but this film can easily be removed by scraping the cup with a sharp instrument and a clean surface insured

#### CONCLUSIONS

The construction of a clip-on electrode is described. This type of electrode has a particular advantage over the more common solder pellet electrode in that it eliminates the usual application of collodion, thereby saving a great deal of time. This electrode can be simply and quickly applied to the scalp without discomfort to the patient. Simultaneous recordings made with solder pellet and clip-on electrodes were found to be identical.

Yale University School of Medicine

## Obituaries

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CLEMENT BUCHANAN MASSON, M D

1898-1946

Dr Clement Masson, who became acting chief of neurological surgery in the Neurological Institute of New York on July 1, 1946, died on Sept 5, 1946 of coronary occlusion at the age of 48. Having served on the house staff of the Neurological Institute from 1925 to 1927, he was the first of the Neurological Institute-trained neurosurgeons to be invited to join the attending staff, and served continuously for nineteen years. His background of neurologic experience and his enjoyment of service under inspired teachers of organic neurology allowed him to carry on the traditional clinical approach to neurosurgical problems, stimulating the younger men on the service with the same spirit with which his predecessors had imbued him.

Dr Masson was born in Newburgh, N Y, of Scottish ancestry, in which he took great pride. His academic training was in Washington College, Washington, D C, from which he received the degree of Bachelor of Science in 1921, after he had received his four years of medical training and the degree of Doctor of Medicine at George Washington University Medical School. He then interned for one and one-half years at St Elizabeths Hospital, Washington, D C, for two years at St Luke's Hospital, New York, and for two years in the Neurological Institute of New York. He became an assistant surgeon in the Neurological Institute of New York in 1927 and assistant in neurology in the Columbia University College of Physicians and Surgeons in 1928 and progressed through successive grades of promotion in these two institutions, being respectively attending neurologic surgeon and assistant clinical professor of neurologic surgery at his death.

Dr Masson was not a prolific contributor to the neurosurgical literature, but his report on "Complete Removal of Two Tumors of the Third Ventricle" (*Arch Surg* 28:527 [March] 1934) is, in a way, a gauge of the cautious, constructive and realistic approach he used in attacking the great technical and therapeutic problems of his special field, and of the increasing confidence which it earned him among his colleagues in the Neurological Institute and in the many hospitals surrounding the city in which he consulted. His studies on "The Parasagittal Gliomas" and "The Differential Diagnosis of Parasagittal Gliomas and Parasagittal Meningiomas" (*Bull Neurol Inst New York* 3:546 [March] 1934 and 5:218 [Aug] 1936), and his unpublished

studies of the importance and significance of the vestibular tests in the differentiation of lesions in the posterior fossa permitted him to contribute much to the lore and the judgment of the succession of house officers who received practical training under him

His independent observations in a series of cases concomitant with those of the late Dr Cornelius Dyke and Dr Leo Davidoff led to their combined publication of the rather important paper on "Cerebral Hemiatrophy with Homolateral Hypertrophy of the Skull and Sinuses," (*Surg, Gynec & Obst* 57: 588 [Nov ] 1933)

Dr Masson was a fellow of the American College of Surgeons and was certified by the American Board of Neurological Surgery He was a member of the St Andrews Society

He was attending neurologic surgeon at Grasslands Hospital, Valhalla, N Y , Pilgrim State Hospital, and Rockland State Hospital He was consultant neurologic surgeon at Northern Westchester Hospital, Mount Kisco, N Y , Vassar Brothers Hospital, Poughkeepsie, N Y , and Staten Island Hospital and St Vincent's Hospital, Staten Island

To many of us in whose progress Dr. Masson was genuinely interested and to whom, in an impersonal metropolis, he provided a measure of fellowship and an example of a successful career based on a well tempered personality, his untimely passing has been a great shock By the many to whom his measured opinion, his constant readiness and his seemingly boundless capacity to serve have been a boon, his loss has been keenly felt

FRITZ CRAMER, M D

# News and Comment

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## THE SCIENTIFIC EXHIBIT, ATLANTIC CITY SESSION OF THE AMERICAN MEDICAL ASSOCIATION

At the Atlantic City Session, June 9 to 13, 1947, the American Medical Association will observe its centennial anniversary. For almost half of those hundred years—since 1899—the Scientific Exhibit has been a feature of each annual session and has developed into a short course in graduate medical instruction.

Exhibits at the 1947 Session will cover all phases of medicine. A certain amount of historical material will be included, but emphasis will be placed on the latest developments of medical science. The representative to the Scientific Exhibit from the Section on Nervous and Mental Diseases is Dr. A. B. Baker, University of Minnesota Medical School, Minneapolis.

Applications for space should be submitted as early as possible, since the closing date is Jan. 13, 1947. Application blanks may be obtained either from Dr. Baker or from the Director, Scientific Exhibit, American Medical Association, 535 North Dearborn Street, Chicago 10.

## AMERICAN BOARD OF NEUROLOGICAL SURGERY

The following candidates were recently granted certificates by the American Board of Neurological Surgery:

Oct. 13, 1946: George Ehni, Temple, Texas; Howard H. Karr, Chattanooga, Tenn.

Oct. 14, 1946: John T. B. Carmody, Worcester, Mass.; Joseph F. Doisey, Boston; J. A. Mufson, Milwaukee; W. W. McKinney, Houston, Texas; Aage Nielsen, Detroit; W. H. Sweet, Boston; Max Taffel, New Haven, Conn.; M. Frank Turney, Brooklyn; Robert D. Whitfield, Albany, N. Y.

Oct. 15, 1946: Charles E. Dowman, Atlanta, Ga.; Antonio Grino, New York; Henry L. Heyl, Hanover, N. H.; Wilfred Risteen, Augusta, Ga.

Dec. 15, 1946: Charles E. Troland, Richmond, Va.

Feb. 1, 1947: Everett F. Hurteau, Memphis, Tenn.; I. Joshua Spicgel, Chicago.

## NORTH PACIFIC SOCIETY OF NEUROLOGY AND PSYCHIATRY

The North Pacific Society of Neurology and Psychiatry held its annual meeting in Portland, Ore., Sept. 20-21, 1946. The following officers were elected for the coming year: president, Dr. Ralph M. Stolzheise, Seattle; vice president, Dr. Frank Turnbull, Vancouver, British Columbia, Canada; and secretary-treasurer, Dr. Herman A. Dickel, Portland, Ore. The executive committee appointed were: Dr. H. Ryle Lewis, Spokane, Wash.; Dr. Gordon Hutton, Vancouver, B. C.; and Dr. Merle Margason, Portland, Ore.

The next meeting of the society will be in Seattle late in March 1947.

Communications may be addressed to Herman A. Dickel, M.D., secretary-treasurer, 707 Medical-Dental Building, Portland 5, Ore.

## SCHOOL OF APPLIED PSYCHOANALYSIS

School of Applied Psychoanalysis. Extension Courses of the New York Psychoanalytic Institute.—The academic year, which extends from Sept. 23, 1946 to June 13, 1947, inclusive, is divided into trimesters of (usually) twelve evenings each. The following courses will be given:

*A For Qualified Physicians*—"Relationship of Physicians and Patients in the Light of Psychoanalysis," Dr Ralph M Kaufman, in cooperation with Dr Harry Weinstock and Dr Sidney Margolin, "Psychoanalysis and Dentistry," Dr Henry M Hart, "Sexual Pathology," Dr Sandor Lorand, "Psychoanalytic Psychopathology," Dr Nathaniel Ross, "Problems of Child Development," Dr Margaret S Mahler, "Indications and Contraindications for Psychoanalytic Psychotherapy," Dr Samuel Atkin, "Principles of Psychosomatic Medicine," Dr Lawrence S Kubie

*B For Nurses*—"Introduction to Psychoanalytic Psychiatry for Nurses," Parts 1 and 2, Dr John Frosch

*C For Social Workers*—"Case Seminar for Psychiatric Social Workers" Part 1 by Dr I P Glauber and Dr Abram Blau, Part 2 by Dr Abram Blau and Dr I P Glauber

*D For Psychologists*—Study Group in "Psychologic Diagnostics," Dr Lawrence-S Kubie, study group in "Psychoanalytic Psychology," Dr Heinz Hartmann, Dr Ernst Kris, Dr Rudolph Loewenstein and Dr Rene Spitz

*E For Sociologists*—Study groups in "Psychoanalysis and Sociology" and "Psychoanalysis and the Social Sciences," Dr Robert Waelder (both these courses under consideration)

#### PENNSYLVANIA PSYCHIATRIC SOCIETY

The eighth annual dinner meeting of the Pennsylvania Psychiatric Society was held at the Barclay, Philadelphia, on Oct 10, 1946

Former United States Supreme Court Justice Owen J Roberts spoke on "What the Layman Can Do About Mental Illness"

The following officers were elected to serve for the year 1946-1947 president, Charles H Henninger, M D, Pittsburgh, president elect, LeRoy M A Maeder, M D, Philadelphia, and secretary-treasurer, Philip Q Roche, M D, Philadelphia

Councillors elected were For two years, Samuel B Hadden, M D, Philadelphia, Harold L Mitchell, M D, Pittsburgh, and Howard K Petry, M D, Harrisburg, Pa For one year, Bernard J Alpers, M D, Philadelphia, Kenneth E Appel, M D, Philadelphia, Thomas A Rutherford, M D, Waymart, Pa, and Cornelius C Wholey, M D, Pittsburgh

Auditors elected were For three years, Elmer V Eyman, M D, Philadelphia, for two years, Robert J Phifer, M D, Woodville, Pa, and for one year, Harry F Hoffman, M D, Allentown, Pa



# Abstracts from Current Literature

EDITED BY DR BERNARD J ALPERS

## Physiology and Biochemistry

DEMONSTRATION OF VISCERAL PAIN BY DETERMINATION OF SKIN POTENTIALS  
LESTER M MORRISON and ERNEST A SPIEGEL, *Ann Int Med* **22** 827  
(June) 1945

Morrison and Spiegel report their observations on 72 subjects in an effort to determine whether viscerogalvanic reaction may be an aid in the differential diagnosis of the pain of organic visceral disease and that of nonorganic disorders. The method employed is a variation of the technic described by Spiegel and Wohl. In this method a known variable potential is opposed to the unknown skin potential.

The authors conclude that the study of skin potentials is an objective method useful in the evaluation of visceral pain. In 74 per cent of the 31 patients with pain accompanying proved organic visceral disease the skin potentials in the corresponding dermatomes were increased over those in the rest of the body by 10 or more millivolts. Of 27 patients with pain of psychogenic origin or pain associated with healed organic disease, 2 showed increases in potential of 8 and 9 millivolts, respectively, while the other 25 had no increase of potentials.

An increase in skin potentials of 10 millivolts or over in the dermatomes corresponding to an organ causing pain supports the assumption of organic disease. Absence of increased potentials does not exclude organic disease. After apparent clinical healing of organic visceral disease, increased potentials may still persist, indicating latent pathologic changes.

GUTTMAN, Philadelphia

NERVE REGENERATION IN THE RAT FOLLOWING TUBULAR SPLICING OF SEVERED NERVES  
P WEISS, *Arch Surg* **46** 525 (April) 1943

Weiss describes a new method of union of severed peripheral nerves which in animal experiments (23 rats) has proved superior to the conventional nerve suture and may be adaptable to human surgery. The method, which should not be confused with the old "tubulization" technic, consists in splicing the two ends of a severed nerve by inserting them into a closely fitting sleeve of a live artery. The use of the arterial sheath eliminates the need of foreign suture material, which may impair nerve regeneration. The tensile strength obtained by the arterial method of nerve splicing is greater than that of the sutureless union of nerves by blood plasma. The utilization of an artery in nerve splicing is particularly suited for nerves too small for suture. The arterial link permits leaving a slight gap between the nerve ends, which seems to create favorable conditions for nerve regeneration. Longitudinal stresses are transmitted through the tissue matrix filling the gap between the two nerve ends and produce parallel orientation of the regenerating nerve fibers. Thus, an orderly regeneration of nerve fibers is assured, and a good functional result may be expected. Histologic study showed that the nerve fibers regenerate in parallel rows, without irregular branching or formation of neuroma or scar tissue. The region of the gap is discernible only by the absence of perineurium. A count of nerve fibers revealed close correspondence between the number of fibers in the proximal stump and the number of regenerated fibers in the gap, but there was a drop in the fiber count in the distal stump. Only a few physiologic observations were made on the functional recovery of spliced nerves. Return of muscle power, measured by isometric recording

after supermaximal stimulation of the spliced nerve, showed return to normal contraction in some instances as early as ten weeks, in other cases the muscular contraction remained deficient, even though there was histologic evidence of good regeneration. Coordination remained poor, in spite of good motor and sensory recovery. This was presumably due to random redistribution of regenerated fibers. Some arterial nerve splicings failed because of improper width of the artery or trauma to the arterial wall. In these cases, fibrosis and irregular regeneration of nerve fibers occurred, or nerve fibers escaped through a defect in the arterial wall.

LIST, Ann Arbor, Mich

CONVULSIVE FACTOR IN COMMERCIAL PENICILLIN. A. EARL WALKER and HERBERT C. JOHNSON, Arch Surg **50** 69 (Feb) 1945

Walker and Johnson studied the effect of commercial penicillin applied topically to the cerebral cortex of the cat, dog, monkey and man. In the cat, as little as 1,000 to 2,000 Oxford units of penicillin may cause convulsive manifestations, in man the convulsive threshold is approximately 10,000 or 20,000 units. The convulsive and antibiotic factors of penicillin appear to be closely related, for they are about equally affected by aging, boiling and acidifying the penicillin solution and by dissolving the penicillin in alcohol.

LIST, Ann Arbor, Mich

INHIBITION OF BRAIN RESPIRATION BY PICROTOXIN. J. R. KLEIN, J Biol Chem **151** 651, 1943

Although the stimulatory effect of picrotoxin on the central nervous system is well known, there is little information concerning the effect of the drug on the metabolism of brain. The respiration of a cat brain preparation and the oxidation of glutamate, succinate, fumarate and pyruvate by the preparation in vitro were inhibited by picrotoxin. The effect of the drug on glutamate and succinate was probably due to an inhibition of the oxidation of fumarate or pyruvate rather than its action on the first stages in the oxidation of the former substances. The effect of picrotoxin on the oxidation of pyruvate may have been due to inhibition of fumarate catalysis, since fumarate decreased the extent of inhibition.

PAGE, Cleveland

A PARALLELISM BETWEEN THE QUANTITATIVE INCIDENCE OF CARBONIC ANHYDRASE AND FUNCTIONAL LEVELS OF THE CENTRAL NERVOUS SYSTEM. W. ASHBY, J Biol Chem **152** 235, 1944

Since it has been shown that the greater amount of carbonic anhydrase per gram in the functionally dominant cerebral area than in the cord is not dependent on any anatomic distribution of gray and white matter, the possibility is suggested that the relation may be due to differences in the amount of enzyme contained in the neurons entering into the composition of the respective areas. This might be true regardless of whether the cell processes or the cell body of the neuron establishes the preponderance of the enzyme. On this basis, it is probable that the carbonic anhydrase content may bear a relation to the factors which cause the functional dominance of the cerebrum over the cord. As a second possibility, the carbonic anhydrase may not be distributed in the neurons but may exist in some accessory cells, which may be more numerous in the cerebrum than in the cord. The content of carbonic anhydrase in the cerebral tissue and in the cord tissue has now been compared. The content of the cerebral tissue was approximately twice that of the cord. Seven species of animals were studied. By separate determinations of the enzyme content of the white matter of specimens of the human cerebrum, it was shown that the greater amount of enzyme in the cerebrum is not due to the larger proportion of gray matter present.

PAGE, Cleveland

CHOREIFORM MOVEMENTS IN A DOG SUFFERING FROM CORTICO-STRIATAL DISEASE.  
HSIANG-TUNG CHANG, *J Neurophysiol* 8:89 (March) 1945

Chang described a male dog with nodding movements of the head and rapid, involuntary twitchings of the left hindleg. The animal demonstrated a postural disturbance in that he could not curl his trunk, and he also could not properly scratch himself. These difficulties were ascribed to rigidity of the muscles. In addition, there was some motor deficit. During a three month period of observation the disturbances were stationary. With the animal under anesthesia, it was noted that excitability of the right motor cortex was decreased. Histopathologic examination of the brain revealed congestion of the cerebral blood vessels, some endothelial proliferation in the walls of the blood vessels, infiltration of the meninges and evidence of encephalitis. The encephalitic lesions consisted of perivascular lymphocytic infiltration and gliosis. The lesions occurred in the left putamen and the adjacent insular cortex and in the right hemisphere in the region of the posterior sigmoid gyrus. In the last area the outer layers of the cortex were not involved, and the giant pyramidal cells were spared. Chang concludes that for the production of choreiform movements preservation of part of the motor cortex is necessary but that both motor cortex and putamen must be damaged.

FORSTER, Philadelphia

ELECTROENCEPHALOGRAM OF DIFFERENT CORTICAL REGIONS OF NORMAL AND ANESTHETIZED CATS. SAM L. CLARK and JAMES W. WARD, *J Neurophysiol* 8:99 (March) 1945

Clark and Ward, employing concentric, implanted leads with the stigmatic portion in contact with the brain, studied the electrical activity of the cat cortex and obtained specific patterns from the frontal and occipital regions and from the vertex. Records from the temporal region and from the pyramids showed less characteristic differences. The onset of sleep was accompanied with the appearance of trains of waves of 5 to 7 cycles per second from the occipital leads. When sleep deepened, the frontal region presented 12 to 14 cycle per second spindles, and random slow activity appeared in all leads. Records obtained during sleep induced with pentobarbital resembled those obtained during normal sleep except that the stages followed each other more rapidly in the former. Activation patterns could be produced by stimuli in normal or in light pentobarbital sleep, but with the animal under deep pentobarbital anesthesia no visible changes occurred in the electroencephalogram during operative procedures. Clark and Ward demonstrated that temporary habituation to a standard stimulus in the normal resting animal produces in the electroencephalogram progressively greater shortening of the period of activation. Alteration of the type of stimulus immediately restores the activation response.

FORSTER, Philadelphia

PROJECTION OF THE RETINA ON THE SUPERIOR COLLICULUS OF CATS. JULIA T. APTER, *J Neurophysiol* 8:123 (March) 1945

Apter studied the electric action potentials obtained from the surface of the superior colliculus of the cat. The potentials were evoked by stimulating spots of known position on the retina, and the stimuli used were short flashes of light. She found a systematic projection of the nasal field, or temporal half of the retina, of the left eye on the left superior colliculus and of the temporal field, or nasal half of the retina, of the right eye on the right superior colliculus. The nasal half of the left area centralis projected only on the right superior colliculus, and the temporal half of the left area centralis projected only on the left superior colliculus. The upper field, or lower half of the retina, was projected on the superior colliculus medial to the lower field, or upper half of the retina. Points along the vertical meridian were projected at the anterior end of the superior colliculus. Points 110 degrees temporal to the vertical meridian of the visual field

of the left eye were at the posterior end of the right superior colliculus, and points 90 degrees nasal to the vertical meridian were at the posterior end of the left superior colliculus

FORSTER, Philadelphia

### Neuropathology

FATAL POISONING FROM POTASSIUM THIOCYANATE USED IN TREATMENT OF HYPERTENSION ANTONIO DEL SOLAR, GASTON DUSSAILLANT, MOISES BRODSKY and GUILLERMO RODRIGUEZ, Arch Int Med 75 241 (April) 1945

The authors report a case of a 53 year old white man with hypertension who was treated with potassium thiocyanate. During the course of treatment he showed mental dulness and increased dysarthria. This was followed by zoopsia and slightly clonic contractures of the upper extremities. Thiocyanate levels in the blood reached 29 mg per hundred cubic centimeters, and the urinary concentration of the drug was 33 mg per hundred cubic centimeters. It was then discovered that for about eight or ten days the patient had been taking as much as 1.34 Gm of potassium thiocyanate a day because he had broken the tip of the dropper. Various supportive measures were attempted after the patient went into coma, but in about two weeks he died.

Necropsy revealed no recent lesions which could account for his death. There were two old areas of encephalomalacia. It is possible that the thiocyanate intoxication came on more readily because of old cerebral damage. A prominent observation in the postmortem examination was an area of acute nephrotic necrosis, which had apparently been asymptomatic during life.

This is the seventh reported instance of death due to therapeutic use of potassium thiocyanate for hypertension.

GUTTMAN, Philadelphia

PRIMARY DEGENERATION OF THE CORPUS CALLOSUM (MARCHIAFAVA-BIGNAMI'S DISEASE) H. HOUSTON MERRITT and AVERY D. WEISMAN, J Neuropath & Exper Neurol 4 155 (April) 1945

Merritt and Weisman report 2 cases of degeneration of the corpus callosum. The first case was that of a man, aged 50, who was addicted to alcohol and was in a state of poor nutrition. There were associated dementia, transitory hemiparesis, aphasia and convulsions. He had an affective psychosis with a severe obsessive-compulsive component.

Sections of the brain revealed complete cystic degeneration of the middle portion of the corpus callosum. The genu was the most severely affected, although the necrosis extended back to the splenium, where the degenerated tissue consisted of two symmetric areas of reddish softening. The cystic degeneration in the rostral portion of the corpus callosum indicated an older process, while the soft, necrotic character of the bilateral lesions in the posterior part of the body and the splenium suggested a more recent development.

Microscopic observations showed almost complete loss of myelin in the middle lamina of the corpus callosum. At the periphery of the lesion the myelin sheaths had undergone a less degree of damage, they stained poorly and were irregularly swollen and attenuated. The axis-cylinders were relatively intact, even in regions where the demyelination was most advanced. Where cyst formation had occurred, however, all tissue elements were destroyed. Proliferation and hypertrophy of capillary endothelial cells were pronounced, and numerous fat-filled histiocytes infiltrated the affected zone. Gliosis was not well developed.

The second case was that of a man, aged 56, who entered the hospital in a state of stupor. He had sustained a head injury and was in shock. Unfortunately, a complete history could not be obtained, but the patient was blind and deaf and had been living alone. The day prior to admission he had been acting peculiarly, and neighbors thought he was ill. Neurologic examination revealed that the patient was in coma. The arms were flaccid, while both legs were extremely spastic. Tendon reflexes were exaggerated, those on the right side being some-

what more active than those on the left. Plantar responses were flexor. The patient failed to regain consciousness and died.

Examination of the brain disclosed extensive degeneration of the middle zone of the corpus callosum. A thin dorsal and ventral rim of intact tissue remained on either side of the necrotic area. The disease process extended from the genu and the anterior commissure caudally to the splenium.

There were large, symmetric areas of necrosis in the subcortical white matter of the frontal, parietal, temporal and occipital lobes. Each lesion was confluent at some point with the degenerated portion of the corpus callosum. In the temporal lobe, the optic radiations were affected. There was bilateral softening of the middle cerebellar peduncles.

The histologic changes in the corpus callosum in this case were similar to those described in the first case. In the subcortical white matter the affected areas were sharply delineated from the surrounding tissue by many astrocytes. Within the rim of gliosis the myelin sheaths had completely disappeared, only scanty, pyknotic oligodendrocytes, proliferating capillaries and hypertrophic endothelial cells remained. Fat-filled phagocytes were rare. No evidence of inflammation was observed.

In the second case a history of alcoholism could not be verified. The association of blindness and deafness in Marchiafava-Bignami disease has not previously been stressed, and it is of interest that they occurred in connection with extensive damage to the temporal and occipital lobes. The well developed gliosis about the subcortical lesions was an unusual histologic feature.

Merritt and Weisman state that the clinical picture cannot be explained by the callosal lesion but requires postulation of a more diffuse cerebral disorder. Marchiafava-Bignami disease is considered a form of chronic alcoholic encephalopathy, for which an inadequate diet and prolonged alcoholism are necessary antecedents.

GUTTMAN, Philadelphia

#### A STUDY OF THE MECHANISM OF VELOPHARYNGEAL CLOSURE ROBERT HARRINGTON, J. Speech Disorders 9 325, 1944

Detailed dissections of the soft palate and pharynx of 10 cadavers were undertaken. The purpose was to investigate the palatal origin of the pterygopharyngeus muscle. The palatopharyngeus and salpingopharyngeus muscles were also studied. In 8 of 10 cases a palatal origin of the pterygopharyngeus muscle was found to exist. In the majority of cases this bundle consisted of a small strand of fibers which originated near the insertion of the levator palati muscle in the palatal aponeurosis, but in all cases a hamular origin of the muscle was also found. The hamular origin was the better developed and was just inferior to the smaller (palatal) origin. In 8 of 10 cases there were muscle connections between the palatopharyngeus and the pterygopharyngeus muscle.

The results of the study suggest the following conclusions: 1. In addition to its hamular division, the pterygopharyngeus receives fibers which originate in the soft palate. 2. The palatal fibers of the pterygopharyngeus may contribute to mesial movement of the pharyngeal walls during velopharyngeal closure. 3. Muscular connections between the palatopharyngeus and the pterygopharyngeus muscle normally exist. 4. Because of these connections, the approximation of the palatopharyngeus muscles during velopharyngeal closure may contribute to the mesial movement of the lateral pharyngeal walls. 5. In addition to the insertions of the palatopharyngeus muscle into the lateral pharyngeal wall, the salpingopharyngeus muscle may occasionally send fibers to the soft palate. 6. The salpingopharyngeus muscle may contribute to velopharyngeal closure by creating an inbulging of the lateral pharyngeal walls. This muscle may also contribute slightly to the elevation of the soft palate.

Four subjects with cleft palate and 1 subject who had a carcinoma of the left maxillary sinus with radical resection were studied for movement of the velum by roentgenographic and other methods.

The general conclusions from both the anatomic and the physiologic studies are as follows 1 Palatal fibers of the superior constrictor muscle exist and probably account for a part of the anterior and mesial movement of the pharyngeal walls 2 Muscular connections between the palatopharyngeus and the pterygopharyngeus exist and may account for some of the mesial movement of the pharyngeal walls 3 Anatomic relationships of the salpingopharyngeus suggest that this muscle probably acts to raise the velum and to move the lateral walls of the pharynx in a mesial direction 4 Considerable mesial movements of the lateral pharyngeal walls exist 5 Mesial movement occurs over a considerable vertical extent Movement may be greater at a lower level than at the higher position 6 The amount of mesial movement is directly related to the extent of velar elevation 7 The greatest extent of mesial movement appears to occur in the area overlying the salpingopharyngeus muscle 8 Although there are significant differences between certain vowel sounds in regard to velar and mesial pharyngeal movements, these differences are not significant for the anterior movement of the posterior pharyngeal wall 9 The velopharyngeal mechanism does not function as a simple sphincter

PALMER, Wichita, Kan

OLIVOPONTOCEREBELLAR ATROPHY OSCAR LUQUÉ and RAUL PUCHETA MORCILLO,  
Rev argent de neurol y psiquiat 10 17 (March) 1945

The authors report the case of a man aged 57 in whom weakness developed in all four limbs three years before admission, progressive impairment of speech was also observed For eighteen months prior to admission the patient was bedridden because of weakness For a time after the onset the lower limbs became tremulous on his attempting to walk For three months he complained of blurring of vision even during very short periods of fixation There was a history of mild, inconstant dysphagia

Objective examination showed inability to sit up properly, the patient laughed readily, there were marked hypomimia and weakness in both lower branches of the facial nerve, the tongue was flabby and could not be protruded normally, use of the tongue in speech was definitely impaired, the masseter reflexes were exaggerated, no dysphagia was apparent, there was weakness of all the limbs, dysidiadokokinesis was present bilaterally, especially on the left, weakness in the upper extremities was more pronounced on the left, there were dysmetria and dyssynergia in the upper limbs, especially on the left, the tendon reflexes of the arms were hyperactive, the knee jerks were exaggerated, especially on the left, there was a bilateral ankle clonus, which was stronger on the left, the abdominal reflexes were diminished on the left, the Babinski sign was elicited on the left, and there was poor plantar flexion on the right, Oppenheim and Gordon signs were present on the right, dysmetria and asynergia were pronounced in both lower limbs Examination of the spinal fluid revealed nothing abnormal The patient died of pneumonia, five years after admission

Postmortem examination showed evident atrophy of the middle cerebellar peduncles and atrophy of the cerebellum, especially the superior surface Both the vermis and the hemispheres were involved Conspicuous depressions, due to diminution of white substance, were seen in both quadrilateral lobes Histologic examination showed demyelination of almost all the white substance of the cerebellum The intraolivary plexus from which fibers of the superior cerebellar peduncles arise was spared Fibrillary gliosis was observed in the demyelinated areas The dentate nuclei were entirely spared, but some of the cells were abnormally pigmented The myelin fibers deep in the white substance were extensively broken up The association fibers were not so seriously involved The Purkinje cells had disappeared The granular cells were also much diminished in number, apparently in proportion to the extent of involvement of the Purkinje cells The basket cells remained but had become flattened transversely and enlarged vertically as the Purkinje cells disappeared Structures in the granular layer, previously described as dilatations of the axis-cylinders of the Purkinje

cells, are considered by the authors to be their cell bodies pulled out of place. The reasons given for this hypothesis are that intact Purkinje cells are not encountered in the presence of these dilatations, careful histologic studies showed Nissl substance, chromatin and structures resembling nuclei and nucleoli in these structures. There were pallor of the pyramidal tracts in the bulb and cord and disappearance of cells of the olives and of the olivocerebellar fibers. The restiform bodies were about one-fifth the normal size. The whole of the middle cerebellar peduncle had disappeared, with almost all the cells of the pontile nuclei gone and replaced by intense gliosis. The authors believe that the pseudobulbar features were due to impingement of the intense gliosis on the pyramidal tracts in the pons.

SAVITSKY, New York

### Meninges and Blood Vessels

HEPATORENAL FAILURE IN THE WATERHOUSE-FRIDERICHSEN SYNDROME BRUNO A. MARANGONI and VINCENT C. D'AGATI, *Am J M Sc* **207** 385 (March) 1944

Marangoni and D'Agati report 2 new cases of the Waterhouse-Friderichsen syndrome which they encountered in the treatment of 134 cases of meningococcal infection at a station hospital.

The first case was that of a man aged 20 who was admitted to the hospital on Jan. 24, 1943 with a diagnosis of infection of the upper respiratory tract. On the eighth day the patient became desperately ill, he was pallid, apprehensive, restless and in severe shock. Numerous petechiae and purpuric lesions were distributed over the entire body. Facial edema was observed, particularly about the eyes. A blood count revealed 47,250 white cells, with 94 per cent polymorphonuclear leukocytes.

A diagnosis of an overwhelming meningococcemia with adrenal hemorrhages (Waterhouse-Friderichsen syndrome) was made. The patient was given a 5 per cent solution of sodium sulfadiazine intravenously (5.5 Gm. in 111 cc. of sterile distilled water). A total of 80,000 units of meningococcus antitoxin was given intravenously within the first eighteen hours of therapy. Colonies of *Neisseria intracellularis* type II-IIa were grown from the blood culture. The patient died on the eleventh day in the hospital, eighty hours after the onset of the Waterhouse-Friderichsen syndrome.

The most striking observation at autopsy was the appearance of the adrenal glands, which together weighed 15 Gm. They showed hemorrhagic areas, particularly in the left gland. Microscopic examination revealed histologic changes in the adrenals, liver and kidney. The hemorrhages in the adrenals were of varying sizes and involved both the cortical and the medullary area. In the liver, there were engorgement of the central vein and sinusoids and marked dissociation of the hepatic cords, many of the cells showed necrobiosis, and many others were heavily laden with bile pigment. The kidneys showed increased cellularity and avascularity of the glomerular tufts, focal areas of polymorphonuclear infiltration and interstitial edema were observed.

The second case was that of an obese white man aged 20, who was seriously ill but rational and oriented. There was facial edema with puffiness about the eyes. The body was covered with numerous petechial and purpuric areas. The blood pressure was 60 systolic and 40 diastolic. A blood cell count revealed 66,950 white cells, of which 96 per cent were polymorphonuclear leukocytes. The blood culture was positive for *Neisseria intracellularis* type I. A diagnosis of fulminating meningococcemia with adrenal hemorrhages (Waterhouse-Friderichsen syndrome) was made. The patient was given 5.5 Gm. of sodium sulfadiazine intravenously in a 5 per cent solution of sterile distilled water. Within the first twelve hours after admission he received a total of 80,000 units of meningococcus antitoxin intravenously. The course was progressively downhill and the patient died eighty-eight hours after admission to the hospital. The

significant observations at autopsy were moderate congestion of the liver and kidneys. The corticomedullary demarcations of the kidneys were indistinct. The brain revealed marked engorgement of its superficial vessels. The adrenals were hemorrhagic and on microscopic section numerous small hemorrhages were noted involving both the medulla and the cortex. The architecture of the hepatic lobules showed pronounced destructive changes in the central and mid zones. The hepatic cords in these zones were completely destroyed. The authors postulate that their cases represent two clinical stages in the Waterhouse-Friderichsen syndrome. The first, or fulminating, stage is generally recognized and consists of severe shock with circulatory collapse. Survival of this stage ushers in the hitherto undescribed second, or hepatorenal, stage, which is characterized clinically by marked oliguria with azotemia and pathologically by severe toxic hepatitis associated with glomerular and degenerative tubular changes. The life expectancy of the patient is inversely proportional to the degree of adrenal tissue destroyed by hemorrhage.

MICHAELS, A U S

LYMPHOCYTOSIS IN THE CEREBROSPINAL FLUID IRVING L. APPLEBAUM, JOEL SHRAGER and WILLIAM PAFF, *Ann Int Med* **23** 170 (Aug) 1945

Applebaum, Shrager and Paff report their observations on 72 patients from the Canal Zone who had lymphocytosis of the cerebrospinal fluid, due to a variety of etiologic agents.

A résumé of the conditions producing the lymphocytosis and the statistical data for this series is given in the following tabulation.

Diagnosis	No of Patients	Percentage
Meningoencephalitis following mumps	30	41.6
Acute lymphocytic meningitis, benign type (cause undetermined)	17	23.6
Syphilis of central nervous system	7	9.7
Tuberculous meningitis	4	5.6
Chemical meningitis (intrathecal injection of serum, etc.)	3	4.2
Acute encephalitis, cause undetermined	2	2.8
Tetanus	2	2.8
Trauma of brain	1	1.4
Abscess of brain	1	1.4
Cysticercosis of central nervous system	1	1.4
Rabies	1	1.4
Lymphocytic meningitis associated with malaria	1	1.4
Guillain Barre syndrome	1	1.4
Infectious mononucleosis	1	1.4

The clinical patterns of mumps meningoencephalitis and acute benign lymphocytic meningitis are discussed, and the early subsidence of the clinical syndrome with a relative lag in clearing of the pleocytosis was prominent in the cases of both types.

The following clinical classification was submitted as an aid in the differential diagnosis of lymphocytosis in the cerebrospinal fluid.

Acute lymphocytic meningitis (benign)

Acute lymphocytic choriomeningitis

Lymphocytic meningitis due to allied viruses

Aseptic meningitis, cause undetermined (Wallgren)

Other diseases of virus origin

Mumps, acute encephalitis (varieties), poliomyelitis, rabies, herpes (zoster and simplex), common contagions, postvaccination, lymphogranuloma venereum, infectious mononucleosis, Guillain-Barre syndrome



## Specific bacterial infections

Tuberculosis, syphilis, tetanus

## Fungous and parasitical infections (uncommon)

Torula infection, cysticercosis

## Intraspinal infections introduced by chemical substances

Serum, procaine solution, iodized poppyseed oil 40 per cent

## Meningitis sympathica (irritative)

Sequela to trauma of brain, aural infection, subdural abscess, epidural abscess

GUTTMAN, Philadelphia

PNEUMOCOCCAL MENINGITIS RECOVERY WITH SULFAMETHAZINE [SULFAMEZATHINE] R PAKENHAM-WALSH, *Lancet* 1 649 (May 22) 1943

The author reports the case of a woman aged 68 with pneumococcal meningitis, as proved by smear and culture of the spinal fluid. She received 2 Gm of sulfamezathine every four hours for five doses, the administration starting the second day of the clinical disease. The third day the dose was changed to 1 Gm every six hours, this dosage was continued for five days, when she showed signs of cyanosis and use of the drug was stopped. The signs and symptoms subsided a few days later and she was able to walk unaided about the room in a month, but the pleocytosis persisted. She was given 15 Gm of sulfamezathine three times a day for a week, but the pleocytosis persisted and was still present three months after the onset of the illness.

McCARTER, Philadelphia

## Diseases of the Brain

TICK-BORNE ENCEPHALITIS ANATOL A SMORODINTSEV, *Am Rev Soviet Med.* 1 400 (June) 1944

Smorodintsev reviews some of the studies on spring-summer, or tick-borne, encephalitis. The incubation period is eight to eighteen days. The onset is associated with elevation of temperature, headache, pains in the neck, vertigo and vomiting. Meningeal and focal neurologic signs, followed by paresis and paralysis of the limbs, back and neck, predominate. An ascending type of paralysis with subsequent bulbar involvement develops. The average duration of the acute phase is five to six days, but the acute stage may run its course in two to ten days. The mortality rate ranges from 20 to 30 per cent. Death usually occurs between the third and the eighth day of the disease. Many patients are physically disabled by paralysis and atrophy of the cervical muscles and shoulder girdle. The patients who recover do not display Parkinson's syndrome, which occurs after von Economo's lethargic encephalitis. Spring-summer encephalitis in the European part of the Soviet Union is marked by a milder course, less invalidism and chronicity, with a mortality rate of only 10 per cent.

The histopathology of spring-summer encephalitis is characterized by intense inflammatory and degenerative changes of the nervous system. The pia mater of both the brain and the spinal cord is always involved. An acute serous exudate appears on the meninges, the brain is softened and congested, and numerous hemorrhages appear in the brain stem, the medulla and the horns of the spinal cord. The most extensive lesions occur in the gray matter of the cord and medulla, fewer in the gray matter of the base of the brain and only slight changes in the cortex. The changes consist in acute perivascular infiltration involving the brain stem and meninges and diffuse or focal infiltration of the gray matter. The disease may be classified as acute nonsuppurative meningoencephalopolioomyelitis.

The causative agent is a virus which passes through the finest Berkefeld and Chamberland filters. Monkeys, goats, sheep and white mice and other rodents

are susceptible to the virus. Mice infected with the spring-summer encephalitis virus react like those infected with strains of the St. Louis and the Japanese encephalitis virus. The virus belongs to type B of seasonal encephalitis and cannot be neutralized by the serums of patients recovered from von Economo's lethargic encephalitis. It also differs strikingly from the virus of the St. Louis type in its antigenic and immunogenic properties, since they do not give cross neutralization or immunity. There are antigenic factors common to both the spring-summer and the Japanese encephalitis virus. According to recent observations by Casals, the virus of spring-summer encephalitis bears a close relation to the virus of louping ill through reactions to complement fixation, neutralization and intraperitoneal cross resistance tests, while intracerebral cross resistance tests give negative results. Neither the virus of Russian encephalitis nor the virus of louping ill appears to be related to the viruses of the Japanese, St. Louis and West Nile types of encephalitis.

The virus of spring-summer encephalitis propagates *in vitro* in cultures of minced chick embryo tissue or when inoculated in developing eggs. The amount of the virus cultured in the egg is distinctly less than that produced in the brain of infected mice.

The systematic increase of specific antibodies in the blood of convalescent patients confirms the role of the virus as the specific causative agent of spring-summer encephalitis. The blood of convalescent persons contains specific antibodies, which are present many years after the initial illness.

The virus of tick-borne encephalitis is indigenous to the forest regions of the Far East, Siberia and the European part of the Soviet Union, the Urals, Karelia, Western Ukraine and White Russia. The disease is distinctly seasonal, beginning at the end of April, assuming epidemic proportions in May and reaching an incidence of 80 per cent between the middle of May and June. Before May and after August only sporadic cases occur. Moderate atmospheric temperature and relatively high humidity favor the development of the disease. The clinical and epidemiologic characteristics of tick-borne encephalitis distinguish it from the Japanese and the St. Louis type, which are most prevalent during the dry, hot summer months of August and September. In Japan and the United States the disease occurs not only in agricultural districts but also in dry, hilly, urban areas, favors no single occupational group and primarily affects persons over 40 years of age. The epidemiologic evidence suggests that the propagation of encephalitis among human beings should be attributed not to contact transmission of the infection but to vectors, such as the blood-sucking arthropods inhabiting the forests, the wood ticks.

The mortality rate of spring-summer encephalitis does not exceed 30 per cent, whereas the mortality rate of summer encephalitis B reaches 60 to 70 per cent and that of the St. Louis form averages 20 per cent. A considerable number of convalescent patients retain residual organic lesions, which is rare with the B and St. Louis forms.

Data are presented which indicate that transmission of the disease is through ticks (*Ixodes persulcatus*). The transmission of the virus in the encephalitis area may be traced from spontaneously infected larvae and nymphs to rodents or birds, which have a latent or clinical form of encephalitis. These rodents, in turn, transmit the virus to healthy larvae and nymphs, thus completing the cycle.

Prophylactic measures aimed primarily at liquidating ticks and rodents are outlined. Immunization with vaccine prepared from the brains of affected animals and inactivated with solution of formaldehyde is one of the most reliable methods. Evidence is presented which shows the value of use of the formaldehyde-inactivated vaccine as a prophylactic measure. Patients with spring-summer encephalitis were treated with repeated administration of convalescent serum and showed definite improvement.

GUTTMAN, Philadelphia

BRAIN ABSCESS ASSOCIATED WITH CONGENITAL HEART DISEASE STANLEY L. ROBBINS, Arch Int Med 75 279 (May) 1945

Robbins reports 3 cases of brain abscess associated with septal defects of the heart. They were selected from the necropsy material, comprising 7,080 cases, at the Mallory Institute of Pathology of the Boston City Hospital during the years 1936 to 1943. This material included 53 cases of congenital heart disease of all types.

The first case reported was that of a 10 year old girl who had a history of listlessness and extreme lethargy for seven days. There was also a persistent cough for three or four days, followed by intractable vomiting. The child died seven hours after admission, after a series of convulsions. Necropsy revealed evidence of congenital heart disease and an abscess in the left parieto-occipital region. The abscess contained, besides streptococci with alpha hemolysis, obvious oral organisms, namely, fusiform bacilli and spirochetes. No path of extension from the oral cavity to the brain and no recognizable origin for infected emboli could be found.

The second case was that of a 19 year old Negro woman who had had several previous admissions to the hospital. She had syphilis and was also diabetic. She entered the hospital with acute glossitis. During treatment for her infection and diabetes left-sided seizures developed, with a residual left hemiparesis and coma. The spinal fluid showed evidence of infection, culture revealing an atypical streptococcus with alpha to gamma hemolysis. Blood cultures repeatedly failed to yield any organism. The suddenness and the dramatic character of the onset led clinical observers to the conclusion either that a cerebral embolism, primary site unknown, had developed or that there was an intravascular thrombosis. The possibility of a brain abscess was apparently not considered. Although no obvious focus for the origin of the septic emboli could be found either clinically or pathologically, the infections of the mouth and lungs must both be considered as possible points of origin. Autopsy revealed an abscess of the right parieto-occipital area, which communicated with the lateral ventricle. The heart exhibited multiple congenital defects.

The third case was that of a 20 year old white woman who was known to have had congenital heart disease. Two weeks prior to admission she began to experience intermittent headaches, which became constant four days before she entered the hospital. The headaches were accompanied with nausea and projectile vomiting. Although she believed that she had had some fever, she experienced no chills. She had clinical and laboratory evidence of meningitis. However, it should be noted that at no time did a culture of the spinal fluid reveal organisms, although on one occasion gram-negative cocci were reported to have been seen on smear. The patient died twenty-four hours after admission to the hospital. At autopsy the only pertinent observations related to the heart and brain. The tetralogy of Fallot was present. In the brain there was a small abscess in the left superior temporal convolution. At one point the abscess communicated with the lateral ventricle in the subarachnoid space. As in the previous case, the underlying brain abscess was entirely unsuspected.

Three cases of cerebral abscess complicating congenital septal defects of the heart are added to those previously reported, bringing the total number of such cases in the literature to 26. In only 3 cases in the literature has an antemortem diagnosis of the disease been made and surgical drainage been instituted, a proportion which reflects principally the difficulty in diagnosis, arising in most instances from unfamiliarity with this complication of septal defects of the heart.

With the increased number of cases reported, it is to be hoped that in cases of congenital heart disease, especially those with the tetralogy of Fallot, underlying brain abscess will be considered in the diagnosis of any focal neurologic damage or meningitis. Certainly, only early recognition will permit successful surgical intervention and hope for cure of this uncommon syndrome.

GUTTMAN, Philadelphia

AMBLYOPIA RESULTING FROM HEMORRHAGE RONALD A COX, Arch Ophth **32**  
368 (Nov) 1944

Occasionally after profuse distant hemorrhage there is noticed immediately, or, more frequently, after the lapse of days, a sudden diminution of vision, which often goes on to complete and permanent blindness, with the ophthalmoscopic picture of atrophy of the optic nerves. Many theories as to the pathogenesis of the condition have been offered. Von Graefe specifically assumed that hemorrhage into the optic nerve sheaths was the cause. Westhoff and Ziegler stated the belief that the loss of vision was due to primary fatty degeneration of the optic nerve induced by ischemia. Hoffman attributed the amblyopia and subsequent atrophy of the optic nerve to retrobulbar neuritis. Leber stated that the ocular changes were produced not only by direct loss of blood but also by retardation of the circulation, which resulted in edema and multiple hemorrhages in the retina. Goerlitz ascribed the condition to foci of degeneration, probably of thrombotic origin, behind the lamina cribrosa. Wolff stated that this type of amblyopia was due to spasm of the arteries, resulting from lack of oxygen. Moore, in discussing Wolff's paper, suggested that the unilaterality observable in some cases indicated a greater tendency to vascular spasm on one side of the body than on the other, such as occurs in migraine. Hartmann and Parfonry stated that the efficacy of vasodilator therapy indicated that vasoconstriction was the cause of the amblyopia. Groenouw asserted that persons who present amblyopia after hemorrhage have previously been ill and that a latent toxin manifests its effect by producing blindness immediately after the hemorrhage. Holden stated that the process is peripheral and that the cause must lie in some product formed in the restoration of lost blood which is toxic under certain conditions. Duggan stated that the toxin responsible for the amblyopia following hemorrhage is a vasoconstrictor.

Regardless of specific pathogenesis, deprivation of blood if sufficiently prolonged will cause loss or impairment of function. The case which the author reports was one of severe hemorrhage following a serious trauma. SPALTH, Philadelphia

"VIBRATION SENSE" AS A DIFFERENTIAL DIAGNOSTIC SIGN IN DOUBTFUL CASES  
OF PARKINSONIAN SYNDROME ALFRED GORDON, J Nerv & Ment Dis **101**  
589 (June) 1945

In cases of unilateral parkinsonism, such as is seen after cerebral trauma, there is frequently ground for diagnostic doubt, and in these instances Gordon has found that hypersensitivity to the oscillations of the tuning fork is present on the affected side. The test is especially useful in differentiating parkinsonism from hysteria, and the author suggests that it may have medicolegal value.

CHODOFF, Langley Field, Va

RELATIONSHIP OF INTRACRANIAL PRESSURE AND PRESENCE OF BLOOD IN THE CEREBROSPINAL FLUID TO THE OCCURRENCE OF HEADACHES IN PATIENTS WITH  
INJURIES TO THE HEAD A P FRIEDMAN and H H MERRITT, J Nerv &  
Ment Dis **102** 1 (July) 1945

Friedman and Merritt report data concerning the cerebrospinal fluid pressure and the presence of blood in the cerebrospinal fluid immediately following injury in 265 patients with acute head trauma and correlate their findings with the occurrence of headaches for periods varying from two to twelve months after the injury. The pressure was less than 160 mm in 56 per cent of patients, 160 to 200 mm in 22 per cent, 200 to 250 mm in 17 per cent and over 250 mm in 5 per cent, while the cerebrospinal fluid was clear in 65 per cent and bloody in 33 per cent. There was a high degree of correlation between abnormalities of the cerebrospinal fluids of either type and the duration of coma and amnesia after injury. In general, the number of headaches, in either the immediate or the late post-traumatic period, did not vary significantly in patients with and without abnormalities of the spinal fluid.

CHODOFF, Langley Field, Va

MACROSTEREOGNOSIA L HALPERN, J Nerv & Ment Dis **102** 260 (Sept) 1945

Halpern reports a new phenomenon which he terms macrostereognosis in the case of a 47 year old man who displayed the sudden onset of dizziness and a sensation as though his right arm had been electrified. Neurologic examination revealed left-sided hemihypesthesia with preservation of deep sensation, astereognosis and loss of position sense of the right hand, right-sided hemiparesis, and nystagmus on lateral gaze. About six weeks later he experienced a "freezing" sensation, together with severe, spontaneous painful sensations over the left half of the body. This suggested a lesion of the right thalamus with probable involvement of the left thalamus as well. The right-sided astereognosis gradually regressed, but as it did the following phenomenon appeared. Although the patient was able to recognize objects placed in his right hand, they appeared bulkier and more massive than they did when placed in the left hand. This abnormal perception was not limited to the hand but involved the entire right half of the body. After about a month it gradually disappeared, first from the trunk and then from the hand and fingers, persisting longest in the first three fingers.

Macrostereognosis is explained as a sensory irritation phenomenon and as an example of the "paradox of contrasting effects," which is characteristic of thalamic disorders. It bears an analogy to the already known macropsia, which has been regarded as an isolated occurrence in the pathologic picture of sensory perceptions.

CHODOFF, Langley Field, Va

FACTORS INFLUENCING MORTALITY IN HEAD INJURY HAROLD C VORIS, Radiology **44** 166 (Feb) 1945

Voris reports on an analysis of 2,714 cases of head injury, the total mortality in which was 11 per cent.

The severity of the injury was the most important factor in the prognosis. The age of the patient was equally important, from the age of 40 the mortality increased steadily.

Too much significance should not be attached to the presence of fracture. Although cases of fracture showed a mortality of 16.5 per cent, as compared with a mortality of 9.3 per cent in cases of nonfracture, fracture was present in only 56.7 per cent of the 120 cases of deaths. It is, therefore, not necessary to have immediate roentgenograms of the skull unless depressed fracture, a penetrating wound of the cranial cavity, middle meningeal hemorrhage or fracture involving the nasal sinuses is suspected.

A bloody spinal fluid worsens the prognosis (17 per cent mortality, as against 6.7 per cent mortality with clear spinal fluid), since severe cerebral contusion or laceration is probably present.

A spinal fluid pressure above 140 mm of water carries a graver prognosis (21.5 per cent mortality, as against 6.7 per cent with normal pressure).

Associated injuries of the chest, some or spinal cord definitely raise the mortality rate. This is also true of preexisting chronic cardiovascular and renal disease.

Acute medical complications are additional factors in influencing the mortality. Thus, of 120 fatal cases, pulmonary complications occurred in 18.3 per cent, meningitis in 5.7 per cent and acute cardiovascular renal complications in 7.5 per cent.

In the entire series, there were 20 cases of meningitis, with a mortality of 60 per cent. Treatment consisted essentially in administration of large doses of sulfadiazine until the cell count was normal and the culture was sterile. Sulfadiazine was also administered prophylactically to patients with bleeding or with drainage of spinal fluid from the nose or ear.

TEPLICK, Washington, D C

TUMORS OF THE THIRD VENTRICLE RAFAEL J. BABBINI, RAUL BARCELONE and JUAN B. ALBERTENGO, *Rev argent de neurol y psiquiat* 9 207 (June) 1944

The authors report 6 cases of tumor of the third ventricle, in 2 of which the diagnosis was not verified. There were 2 cases of colloid cyst of the third ventricle, 1 of teratoma and 1 of ependymoma. They emphasize the value of iodoventriculography in the diagnosis of tumors of the third ventricle. In none of the 4 verified cases did recovery occur, in spite of operation. In 2 cases there was paralysis of upward gaze. An unusual feature was a history of epileptic attacks for a few months in a case of colloid cyst of the third ventricle. In 2 cases papilledema was not present, in spite of evident obstruction of the aqueduct of Sylvius. In 2 cases of ependymoma and colloid cyst, there was a long history of bouts of headache, of approximately twenty years' duration. In a nonverified case the ventriculogram showed a tumor of the third ventricle. The patient improved after a rubber tube was inserted to drain the lateral ventricle into the cisterna magna.

SAVITSKY, New York

### Encephalography, Ventriculography, Roentgenography

ANATOMICAL AND PHYSIOLOGICAL CONSIDERATIONS PREREQUISITE TO DIAGNOSIS OF BACK TRAUMA EBEN J. CAREY, *Radiology* 41 554 (Dec) 1943

Slight trauma may disable vertebral bodies which have been repeatedly insulted by postural errors and mechanical strain. The average length of the spinal column is 70 cm, about one-fourth the length being made up of intervertebral disks. The primary curves, persisting from the embryonic axis, are those of the dorsal and the sacral areas. The cervical and lumbar curves are secondary, or accommodation, curves. The lumbar curve appears when the child begins to stand and walk. Physiologic scoliosis, with convexity to the right, is present in the upper dorsal region in right-handed persons.

Persons with anomalies of the spinal column have less stable backs and are more susceptible to trauma. An elongated transverse process of the fifth lumbar vertebra, found in 25 per cent of persons with pain in the lower part of the back, impinges on the ilium and may form a painful bursa. Sacralization of the fifth lumbar vertebra, normally seen in 35 per cent of persons, occurs in 50 per cent of patients with pain in the lower part of the back. Defects in the neural arch, "kissing" spinous processes, abnormal lumbar lordosis, spondylolisthesis and constitutional variations of body build, all predispose to back sprain.

TEPLICK, Philadelphia

DIFFERENTIAL DIAGNOSIS OF TRAUMATIC LESIONS OF THE SPINE S. A. MORTON, *Radiology* 41 560 (Dec) 1943

Morton discusses several conditions of obscure origin which might be concluded on roentgenologic grounds to be the result of a definite injury, but which are probably not of traumatic origin.

Nontraumatic dislocation of the atlantoaxial joint occurs in young persons, accompanying infections of the throat or cervical nodes. It may occur with rheumatic fever. The dislocation is rotary, and usually roentgenograms reveal a definite separation between the odontoid process and the anterior arch of the atlas. Hypertrophic changes of the posterior margins of the cervical vertebrae, with projecting spurs, may produce nuchal pain, radiating down the arms. Oblique views aid in visualizing this condition. Senile osteoporosis, without trauma, may produce a vertebral collapse in the dorsal area. A previous trauma cannot, however, be entirely disregarded.

Scheuermann's disease, or osteochondrosis of the secondary vertebral epiphyses, is fairly common. The characteristic roentgenographic appearance of irregular, wavy upper and lower surfaces of the body, with symmetric wedging, does not

suggest the effects of fracture. Localized epiphysitis, in the lower dorsal or upper lumbar vertebra, occurs in an anterior corner of the body. Increased density, fragmentation and beveling of the vertebral body occurs characteristically. The body of only one vertebra is involved. "Persistent epiphyses," a defect in the upper anterior border of a vertebral body, with a triangular piece of bone above and slightly anterior, is asymptomatic. The cause is unknown. Nuclear molding, or Schmorl's nodes, is a biconcave expansion of the intervertebral disks, seen most commonly in the lumbar area. They are unrelated to injury. Kummell's disease (compression fracture of a vertebra), a post-traumatic rarefaction and collapse of a vertebral body after a latent period, is not an entity established beyond doubt.

TEPLICK, Philadelphia

OSTEOPOROSIS CIRCUMSCRIPTA CRANII FRANK WINDHOLZ, Radiology **44** 14 (Jan) 1945

Windholz reports 3 cases of this condition in none of which the disorders was related to Paget's disease. Case 1 was that of a woman aged 63, and the osteoporosis was part of a well recognized leontiasis ossea, as proved by biopsy. Case 2 concerned a woman aged 58 in whom the osteoporosis was associated with a peculiar osseous condition of the skull present since youth, called fibrous osteodystrophy and appearing clinically as leontiasis. Extensive hyperostoses surrounded the osteoporotic areas. Case 3, that of a woman aged 58, showed the changes in the skull characteristic of osteoporosis circumscripta, with atypical roentgenographic and clinical signs suggestive of hyperparathyroid disease. A few years later the latter diagnosis was firmly established, both clinically and roentgenographically. A parathyroid adenoma was removed.

In the literature, only 60 per cent of the cases of osteoporosis circumscripta were related to Paget's disease. Other associated conditions were leontiasis ossea, bony tumors of the jaw, hyperparathyroidism and tumors of the brain. The author believes that osteoporosis circumscripta is a characteristic reaction of the bones of the cranium and is probably caused by circulatory disturbances in the presence of bony hyperplasias or of bony tumors near the base of the skull.

TEPLICK, Washington, D C

INTRACRANIAL ANGIOGRAPHY C F LIST, C H BURGE and F HODGES, Radiology **45** 1 (July) 1945

Intracranial angiography offers a means of obtaining information of value in cases of suspected intracranial aneurysm and anomalies of intracranial vessels, in certain cases of arterial occlusion and in cases of expanding lesions involving one cerebral hemisphere which have not been accurately localized.

The internal carotid artery supplies intracranial branches to the structures above the tentorium, while the subtentorial portions of the brain are supplied by branches of the vertebral vessels.

For carotid injections, local anesthesia is used, and the common carotid artery is exposed. Whenever feasible, injection is made into the internal carotid artery directly. When the common carotid artery must be used, the external carotid artery is occluded during the injection.

Ordinarily, three injections are made, two to obtain stereoscopic lateral exposures, and the third for a posteroanterior view. The opaque material is forced into the artery as rapidly as possible. When the injection is about two-thirds complete, the first lateral exposure is made. As soon as the film can be changed (about three seconds), a second lateral roentgenogram is made, which records venous return. After irrigation with isotonic solution of three chlorides U S P, the entire procedure is repeated, with the roentgenographic tube shifted for stereoscopic pictures. During the third injection a single posteroanterior exposure is made.

Exposure of the vertebral artery for direct injection is technically difficult. If the vessel is satisfactorily exposed, a direct puncture may be made at the level of the sixth cervical body, retrograde injection into the subclavian artery will indirectly fill the vertebral vessel and its branches.

Despite its radioactivity, a 25 per cent colloid suspension of thorium dioxide in amounts not exceeding 30 cc is the preferred injection medium, giving the best visualization and being virtually nonirritating. The authors believe 30 cc or less is probably without late harmful effects from radioactivity.

TEPLICK, Washington, D C

OSTEOGENIC SARCOMA OF THE SKULL L H GARIAND, Radiology **45** 45 (July) 1945

While secondary sarcomatous degeneration in Paget's disease (osteitis deformans) of the skull is not uncommon, primary osteogenic sarcoma of the skull is extremely rare. The former occurs in persons of the older age groups, when primary osteogenic sarcoma of any bone is unlikely.

A seaman, aged 17, noticed a lump at the base of the skull, which had grown in two months to the size of a ping-pong ball. It caused some limitation of cranial movement and was slightly painful. At a Pacific base hospital a diagnosis of osteochondroma was made and the mass removed. No report of biopsy was available. In about eight weeks the mass recurred, being slightly more painful and reaching about 8 cm in diameter. Roentgenograms of the skull showed extensive thickening of the outer table of the occipital bone, chiefly to the right of the midline, with considerable spiculation and a small amount of irregular calcification in the tumor. The inner table appeared completely normal. A roentgenographic diagnosis of primary osteogenic sarcoma of the occipital bone was made.

The tumor, together with invaded soft tissues and muscles, was excised, and a molded tantalum plate was inserted to replace the bone. The histologic diagnosis was sarcoma, osteoblastic and osteogenic. Despite intensive postoperative irradiation and the excellent condition of the patient one month after irradiation, the outlook was considered hopeless.

TEPLICK, Washington, D C

### Congenital Anomalies

AN UNUSUAL FAMILIAL SYNDROME A P FRIEDMAN and J E ROY, J Nerv & Ment Dis **99** 42 (Jan) 1944

Friedman and Roy report on a family of 6 feebleminded children of parents of average intelligence. Each had a mental age of less than 3 years and presented identical neurologic signs, namely, strabismus, extensor plantar reflexes, speech defect and foot deformity. The parents were cousins, their fathers having been half-brothers. Electroencephalograms of the mother and of all 6 siblings showed a uniform tendency toward high voltage and irregular frequency.

CHODOFF, Langley Field, Va



# Society Transactions

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## BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

Madeline R. Brown, M.D., *Presiding*

*Regular Meeting, April 26, 1945*

**Clinical Implications of the Bellevue-Wechsler Test, with Particular Reference to Cases of Injury to the Brain** DR MILTON GREENBLATT, MISS ROSALINE GOLDMAN and DR GAYLORD P. COON

Experience with the Bellevue-Wechsler test at the Boston Psychopathic Hospital over a period of six years leads us to believe that it is a superior test because it can be administered with relative ease, has been standardized on adults over a wide age range, has the flexibility of a point scale, with the possibility of direct comparison of performance on various test items, and taps a wide range of functions and elicits data of considerable value and interest to the clinician. In cases of the state characterized by the term "brain damage," this test would seem of special value for both diagnosis and investigation.

Two types of signs were found in cases of damage to the brain—quantitative and qualitative. The quantitative signs consisted essentially in a wide discrepancy in the weighted scores of various subtest items. As a rule, performance on nonverbal items (picture arrangement, picture completion and block designs) was most seriously affected, but there was always at least one verbal subtest in which there was loss of ability to function. The qualitative signs were best displayed in the nonverbal test items, in which the patients showed rigidity, inability to shift attention or change the mode of response, inability to ignore superficial or extraneous stimuli and difficulty in organizing material into either a required pattern (block designs) or a meaningful, logical sequence (picture arrangement). In cases in which both quantitative and qualitative irregularities of performance were found, clinical analysis revealed a high incidence of damage to the brain.

Within the broader framework of the "organic" pattern as elicited with the Bellevue-Wechsler test, we noted seven variant configurations, or profiles, which were more or less mutually exclusive. The full significance of these profiles is not yet clear, certainly, they are not specific for any given disease entity. As a rule, the greater the loss of function as displayed in the psychologic examination, the more serious was the cerebral damage. There were suggestive relationships between the particular psychologic configurations and certain groups of symptoms, but the meaning of these trends must await a greater accumulation of cases.

### DISCUSSION

DR FREDERICK WYATT: Of the criticism which traditionally is expected to follow a scientific presentation, I have little to offer. This is an interesting and, from the standpoint of the psychologist at least, a rather successful study. It may have been a surprise that we were not presented with more statistics. Remembering the folkways of psychologists, we might have anticipated blackboards full of figures and tables. The authors should be commended for having emphasized the qualitative aspects of their observations. No quantitative study should be attempted until the possibilities of organizing the material in one's thought and of establishing a tentative framework of reference have been exhausted. To test the most sensible hypothesis is the function of statistics in an investigation like the present one. As I have had a previous opportunity to discuss this paper, I shall sum up its quantitative aspects by saying that the authors might now find it

helpful to apply  $\chi^2$  technics systematically in order to obtain measures of the differential significance of individual results

In 72 per cent of the cases the clinical and psychologic findings were in agreement. The remaining 28 per cent present a problem. How can one account for this disagreement? First, it should not be forgotten that this study grew out of routine clinical work. Patients do not care to take tests, they are full of wiles and offer complex problems for psychologic study, to which I shall return in a moment. The medicoclinical work-up was not always so complete as one would have desired. If one had for all the subjects data from all the clinical tests given to a number of them, the percentage of agreement between clinical and psychologic diagnosis might well have been higher.

In order to evaluate the significance of the 28 per cent disagreement between the two methods, with the diagnosis of "brain damage" by psychologic methods unsupported by medical ones, one must ask oneself what it actually means when psychologists report findings such as those presented here. Primarily, it means only that the subject under scrutiny shows deficiencies in certain types of intellectual action, or in certain aspects and functions of his thinking. In psychologic testing, certain patterns of deficiency were found empirically to concur with the clinically established diagnosis of cerebral damage. On a somewhat more deductive line of reasoning, these deficiencies also seemed to indicate that with impairment of intellectual functions one would expect to encounter inadequate functioning of the brain. This last point, however, while indicating that a brain cannot function at "normal" capacity when operating in such a deficient manner, does not necessarily imply that this inferior performance is due to one of the stark pathologic processes clinically labeled "brain disease."

In accordance with Dr Goldstein's ideas, the aspect of thinking most conspicuously reduced in these cases is the ability to perform abstractions. One might elaborate and add that there is reduction in the ability to analyze a whole or to synthesize parts into a whole, to draw simple inferences from data, to recognize configurations and to fit elements into them correctly, to learn, to retain and to recall from memory. Besides actual cerebral disease, at least two other factors may account for a reduction in at least some of these functions: congenital inferiority, as in feeble-mindedness and probably in some forms of psychopathic personality, and states of emotional conflict causing conditional and temporary disabilities of a somewhat different kind. While the more clearcut of these disturbances can be distinguished rather successfully with the Wechsler-Bellevue test, one need only recall the infinite complexity of psychologic qualities, the fusion and overlaying of character traits and disease syndromes which is the rule, rather than the exception, in our clinical material, to acknowledge that in the 28 per cent the negative clinical diagnosis might be final and the psychologist's statement of an impairment of thinking might still be correct, though it may not spell "brain disease" in the succinct sense of the clinic.

The pattern analysis presented by the authors seems to me a successful step toward further isolating and clarifying the various subpatterns of deficient intellectual functioning and of approximating their clinical meaning. Would it be possible now to go further and to aim toward a more detailed analysis of patterns of performance? If two patterns of test performance are too vaguely similar to be distinguished, yet do not accord at all with corresponding clinical findings, one must assume that there are factors of difference in the results not yet seized on. Could one map out in detail all the mental functions called forth in each of the subtests of the Bellevue scale? Some of the subtests seem to be based on memory and recall only, most are more complex, however. The cube test, for instance, the most sensitive of the Bellevue subtests, involves abstraction, generalization, analysis, synthetic acts and probably more. Could a list of intellectual functions be designed into which a subject's performance could be entered, in terms not of subtest scores but of abilities and disabilities shown in performing these functions? Pattern analysis could thus be put on a much more differential basis. Several subgroups within the somewhat tenuous class of encephalopathic

performances might be isolated, and the test might thus be made a more sensitive instrument of diagnosis

DR KURT GOLDSTEIN This is an interesting and clinically important paper. If I were to say anything, I should question whether it is necessary and useful to employ so many tests. One can often reach the same result in an easier way by careful analysis of the procedure of the patient in one test. That is the case particularly with damage of the function of abstraction. There is scarcely one test which could not be used for this purpose. It is only easier to find the defect with the tests I have proposed. There is an interesting difference in tests as to the amount of endowment the patient needs to fulfil the test and, on the other hand, as to the amount of impairment of some functions, particularly abstraction, which can be hidden by use of endowment. Always, analysis of the procedure by which the test is fulfilled is the most important point, sometimes with use of subtests which impede use of endowment.

DR ANDRAS ANGYAL, Worcester, Mass. This study demonstrates again the value of psychologic test procedures in neurology, particularly in cases in which cortical damage is suspected. In the diagnosis of cerebral damage the Wechsler-Bellevue test is of course not the test of choice. The test, having been devised primarily for a different purpose, includes many items which are not particularly helpful in the diagnosis of cerebral damage. There are, however, some other items in the test in which one is likely to obtain rather characteristic responses in the case of cortical damage. The authors made a contribution of significance in pointing out the characteristics in the results of the Wechsler-Bellevue test which suggest the diagnosis of cerebral damage, the test is being given routinely in many psychiatric hospitals, and it is an advantage to be able to derive useful information in addition to determination of the intelligence level.

DR LEO BERMAN I am interested in the cases of functional disorders included in the study. In what percentage of these cases would you find organic damage to such a degree that it would lead to a change in diagnosis from functional to organic disease?

MISS ROSALINE GOLDMAN It should be emphasized that this whole study is the outgrowth of routine testing at the Boston Psychopathic Hospital. We are required to give psychologic examinations in court cases, and we have suspected cerebral damage in many instances. We feel that a routine psychologic examination gives a great deal of incidental information of great use to the clinician before it is available from other sources. When a psychologist is primarily interested in studying cerebral damage, he will use other tests especially designed for that purpose.

DR MILTON GREENBLATT Concerning the 28 per cent of "problem" cases to which Dr Wyatt referred, I can say that the psychometric test shows no less loss of function in this group than in the group in which clinical corroboration was found. Psychologically, the defects in the 72 per cent group and those in the 28 per cent group were roughly the same. There was no difference in age distribution, so age was not a factor. We did get the impression that the 28 per cent group was worked up less completely than the 72 per cent group. Why were these cases not worked up as well? Probably largely because the indications were not there. If we had tested specifically for cerebral damage, instead of carrying out routine tests, we probably would have found many cases of the 28 per cent group that would fall into the 72 per cent group, thus enlarging the latter. As Dr Angyal mentioned, and in reply to Dr Goldstein's question. This was a routine test and gave data besides those relating to cerebral damage. We wondered how much weight the clinical staff should put on the observations of the psychologists. In 72 per cent of the cases in which the psychologists offered the diagnosis of cerebral damage there was some clinical corroboration. How often is there clinical evidence of damage to the brain when the psychologists say nothing is wrong? We have found it occasionally, but the percentage is very low.

We have not yet analyzed any large series of cases in which the diagnosis was manic-depressive psychosis or schizophrenia. In how many of such cases will these abnormal psychologic responses be found? I agree with Dr. Wyatt that the absence of complete overlap of clinical and psychometric data leaves room for speculation. One may ask the cause of the psychologic disorder found in the 28 per cent group. Factors of endowment and constitutional factors cannot be ruled out. In Wechsler's series taken from the population at large, from which he derives averages which one relies on, in what percentage did these abnormal responses occur? Dr. Goldstein's writings and observations have meant a great deal to us. They have provided significant leads for our psychologists. Whenever in the routine Bellevue test we found suggestive evidence of cerebral damage, we continued our study with the aid of more specific tests, such as those devised by Dr. Goldstein.

**Fatigue in Relation to Adrenal Cortex** DR. GREGORY PINCUS and DR. HUDSON HOAGLAND, Worcester, Mass.

Studies of stress in relation to the output of 17-keto steroids as a measure of the activity of the adrenal cortex were reported, and the effect of administration of certain steroids on fatigue of psychomotor performance was described. The output of 17-keto steroids in psychotic patients and in controls under conditions of stress was also compared.

In the first series of studies, 7 college students were given 67 two to six hour runs, after an adequate learning period, on a serial coordination meter with airplane type controls.

Timed samples of urine were collected before each run and also for the period of the run. After correction for time of day from a curve for the diurnal excretion rhythm, the output of 17-keto steroids under stress, i. e., the mean test value for 17-keto steroids minus the control value, expressed as milligrams excreted per unit of time, was calculated. This value for excretion of 17-keto steroids under stress was found to be correlated to a striking degree with the subject's ability to avoid errors due to increasing fatigue, in that the men showing the lowest output of 17-keto steroids under stress had the fewest errors.

In another series of experiments on an airplane type pursuit meter, anoxia was found to increase the over-all output of 17-keto steroids, in close relation to failure in scoring ability. The output of 17-keto steroids under stress was studied in 16 Army pilots in 152 routine instruction flights and in 7 Pratt and Whitney pilots in 56 test flights. Correlation coefficients of  $>0.95 \pm <0.01$  were found between the per cent of time the pilot was airborne and his output of 17-keto steroids under stress. An independent rating of the fatigability of Army fliers made by their squadron commander correlated significantly with the degree of diuresis during stress.

Attempts were made to find a steroid substance that could be taken orally and that would enhance performance in fatiguing psychomotor operations and which, at the same time, would be harmless.

In a preliminary series of tests, neither oral administration of adrenal cortex extract nor injections of progesterone were accompanied with improvement in pursuit meter scoring, but the administration of  $\Delta^5$ -pregnenolone was effective. Seven Army pilots accordingly made a series of scored runs on an airplane type pursuit meter and were given alternately placebos and  $\Delta^5$ -pregnenolone (50 mg per day), followed by placebos again. A significant improvement in scoring—in absolute score, in decrement measures and in "emergency" performance—occurred during the administration of pregnenolone. These findings were subsequently confirmed by a series of tests on 7 hired civilian subjects, who, although their performance improved with pregnenolone, showed much less improvement than the aviators. In all, 304 tests were made with the 14 men. Those persons under most

stress from their daily work, provided they were striving to make maximum pursuit meter scores, were the ones whose performance improved with pregnenolone. In another series of tests on psychotic patients and on indifferent hospital employees we found no improvement with pregnenolone. These groups were characterized by low incentive and low effort in the tests.

The effect of pregnenolone on industrial production was then studied, and the following observations were reported:

Eight leather cutters were studied over a period of eight weeks. The men received no incentive pay, and the amount of production per se was therefore not a measure of the effects of experimental procedures. The wastage of leather was measured and compared when the men were receiving 45 mg of  $\Delta^5$ -pregnenolone per day and when they were receiving placebos indistinguishable from the pregnenolone pills. Administration of pregnenolone was not found to lessen the wastage in cutting sole leather.

Twelve turret lathe operators (8 men and 4 women) were studied in relation to their daily production of bayonets on a piece work incentive basis when they were receiving pregnenolone and when they were receiving placebos. During administration of the placebos the efficiency of production increased  $10.1 \pm 2.18$  per cent, during administration of pregnenolone the increase was  $18.3 \pm 1.71$  per cent. The difference of 8.2 per cent is three times the standard deviation, and the value of  $P$  is 0.005. The difference is therefore statistically significant.

The number of scrapped bayonets was less by 32.7 per cent when the workers were receiving pregnenolone than when they were receiving placebos, but this difference in figures for scrapped production is not quite statistically significant ( $P=0.06$ ).

On discontinuation of all medication, an increase in efficiency of about 10 per cent remained during the four weeks the production was continued. The role of job stress and incentive was discussed in relation to the findings.

Piece work production of 173 male and female workers making optical goods was studied when they were receiving placebos and when they were receiving pregnenolone. A significant increase of 4.2 per cent in over-all production was found for 77 workers taking 50 mg of  $\Delta^5$ -pregnenolone per day as compared with their previous production levels. This was 1.3 per cent higher than the levels when they were taking placebos, and the difference is statistically significant.

The decrease in wastage and repairs for 39 workers amounted to 18.9 per cent when they were taking pregnenolone and 13.7 per cent when they were taking placebos as compared with their preexperimental levels.

Ninety-six workers were studied for three months. One-third took 70 mg of  $\Delta^5$ -pregnenolone per day in the form of pills, another third took 25 mg per day and a third took 0.1 mg per day (a placebo for all practical purposes). The group receiving 70 mg of pregnenolone showed most pronounced improvement in earnings and in the saving of wastage. The improvement shown by the group receiving 25 mg a day fell between that of the group receiving 70 mg and that of the group receiving 0.1 mg a day. There were thus demonstrated significant differences in dosage in relation to improvement of industrial production resulting from the ingestion of pregnenolone.

Some improvement of production due to pregnenolone tended to be retained after the termination of medication.

A comparison of function of the adrenal cortex in normal and in psychopathic subjects under the stresses of cold, heat, pursuit meter operation and psychologic tests revealed the following facts:

1. A rise in urinary 17-keto steroids during stress, followed by a sharp fall after stress, occurred in normal men, this pattern was not observed in most psychotic subjects.

2 A decrease in the total number of circulating lymphocytes in the blood occurred in normal men (the reduction averaging 25 per cent), but no such decrease was observed in psychotic men, rather, there was a rise (averaging 25 per cent)

These data are interpreted as indicating a failure in response of the adrenal cortex to stress in psychotic men

## DISCUSSION

DR JOSEPH C AUB This is obviously important work. It reminds me of Professor Benedict's studies of fatigue in student examinations. He concluded that it took 2 peanuts' worth of calories to cerebrates actively, that did not explain the fatigue of an hour's examination. This study comes near explaining the fatigue that comes with hard work. It is surprising that the adrenal glands should be so greatly involved. When Selye first described the alarm reaction, I was skeptical about it. One cannot be skeptical about it any more. The point which puzzled me was the prolongation of the immediate rise in excretion of 17-keto steroids with alarm and the production of these substances for weeks afterward. The authors have not shown the speed of recovery of ketosteroids after alarm, if one could call it that—the acute stresses they have been studying. How long is the rate of excretion of 17-keto steroids distorted?

I have nothing new to offer in regard to this work. The only work analogous is that on the deer. My colleagues and I have been studying the growth of deer antlers and the action of 17-keto steroids. We tried to determine the excretion rates but failed. I am interested in the extraordinary psychologic reactions of the deer to injections of the steroids. We have used only testosterone. The deer is a wonderful animal for psychologic study. The male is like the female ten months of the year. He is charming and has none of the unpleasant male characteristics. Then for two months the buck has all the disagreeable characteristics usually manifested by man. He is aggressive and irritable. If one gives a buck testosterone when he is doelike (we wanted to see what the drug would do to the antlers), he becomes like a male. He has all the unpleasant characteristics. One cannot get into the cage with him without being attacked. He is aggressive toward the doe, although it is not the season. He tries to fight, he tears his antlers. If testosterone is injected two months before the antlers start to grow, he shows the same characteristics he would later. A few years ago I talked to this society about the lack of effect of 17-keto steroids and estrogen on the characteristics of maleness and femaleness. The rates of excretion of these substances were the same in girls and boys. Therefore the characteristics of sex were not explained by their rates of excretion. One does change the personality of a buck by the injection of testosterone. It is a potent hormone.

DR O H PEARSON I am not qualified to talk about this subject. My associates and I have taken considerable interest in it, but, unfortunately, we have nothing to report as yet. One phase of the work of Hoagland and Pincus is the use of drugs and the measurement of their effect. I should like to ask what hormonal activity pregnenolone has. It was interesting to note the curves in the measurement of piece work of the subjects, to note that the work increased with administration of placebos. One finds that in all clinical work on drugs, particularly when the exact action of the drug is not known.

DR HALLOWELL DAVIS Did pregnenolone prevent colds?

DR HUDSON HOAGLAND, Worcester, Mass. No, I am sorry to say that it did not. We went over the data and found no correlation.

DR JACOB E FINESINGER The disconcerting thing about the alarm reaction is that almost anything may produce it. Does that hold true with respect to the excretion of ketosteroids? Does the nature of the stress make any difference?

DR JOSEPH C AUB Does it make any difference in the action on the sympathetic nervous system whether the stress situation is pleasant or unpleasant?

DR HUDSON HOAGLAND, Worcester, Mass In reply to Dr Finesinger, we have not found out much about one stress as compared with another We have used various stresses to determine the hormonal involvement In students taking examinations, for example, we observed the ketosteroid response to stress Such stress may be comparable to pursuit meter operation and exposure in a cold room, but we cannot compare its strength We have used the pursuit meter under conditions of anoxia We have found that the lymphocyte count falls, just as it does in a hot room We have not been able to compare one stress with another, except to note that extremely varied stresses seem to make for changes in the output of ketosteroids

DR GREGORY PINCUS, Worcester, Mass To answer Dr Aub's question first We have not measured accurately the latent period between stress and return to normal excretion It would seem in the case of the pursuit meter operation that the effect in a normal person lasts a minimum of two hours Every one of our poststress ketosteroid measurements represent a period of at least two hours, and the values are lower than one would expect if no stress had occurred We have measured the lymphocyte response much more exactly It is over in one or two hours after a stress applied for one hour The 17-keto steroids represent an accumulation of metabolites of adrenal cortex hormones The decrease in lymphocytes represents the action of active hormones of the adrenal cortex, according to White and Doherty If the adrenal cortex extract is injected, the lymphocyte count drops, if normal animals are subjected to stress, it drops, if adrenalectomized animals are subjected to stress, it does not drop

DR JOSEPH C AUB Does it not seem strange that anything so essential as the adrenal cortex should exhaust itself and have a long latent period before it returns to function?

DR GREGORY PINCUS, Worcester, Mass Do you call one or two hours long? If you refer to damage done due to burns, we have no experiments We have only short time experiments I should be interested in studying patients willing to live in a hot room longer They might be more like the patients with burns Why the depressed phase of 17-keto steroid output should continue so long in cases of severe damage is something which has not been answered by any experimentation I know of

DR HUDSON HOAGLAND, Worcester, Mass Mr Fred Elmadgian is doing the stress work on rats The stress consists in tying down the animal After the rat has been tied down, the lymphocyte count falls for several hours After that the count starts to rise, and in ten to fifteen hours it is nearly back to normal, even though the animal is still tied down Animals with the adrenal glands removed do not show any drop in the lymphocyte count

DR GREGORY PINCUS, Worcester, Mass The effect of placebos is well known in industrial experimentation Give workers anything and they do better We were aware of this when we started the investigation, that is why we had the placebo controls I do not know why placebos work

Information is beginning to accumulate on the physiologic action of pregnenolone Selye has shown that it has certain hormonal properties It is unique among steroids in that in large enough doses it has a multiplicity of hormonal properties It acts, for example, as an adrenal cortex steroid and as a progestin It seems to be pharmacologically, as well as hormonally, active Selye's notion, and one we have felt has some basis, is that it is a substance which might be converted in the body into hormonally active steroids In subjects who have taken pregnenolone we find a striking increase in estrogen output in the urine We find evidence for production of progesterone from pregnenolone in vivo We do not know about conversion to adrenal cortex steroids There is no doubt that pregnenolone is pharmacologically active in large doses What we have used is probably a small dose for human subjects We have not explored the limits of the dose Perhaps we should try a wider range There is, however, the matter of expense

DR HUDSON HOAGLAND, Worcester, Mass Torda and Wolff have reported that pregnenolone facilitates the synthesis of acetylcholine Estrone and estradiol also do this, but these are the only three out of many steroids they have examined which are effective One is tempted to speculate whether this factor may play a role in facilitating conduction in the nervous system in relation to fatigue

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Madelaine R Brown, M D , *Presiding*

*Regular Meeting, May 17, 1945*

**Diagnostic Aspects of Unilateral Ruptured Cervical Disk** DR JOST J  
MICHELSEN and DR WILLIAM JASON MIXTER

The data to be presented were collected from 18 cases, in 5 of which lesions existed at the fifth, in 12 at the sixth and in 1 at the seventh interspace In 12 cases the left side was involved The chief complaint was pain associated with paresthesias in the region of the scapula, arm and hand, of two weeks' to two years' duration Remissions in cases of a long-standing condition were common Two types of pain were observed All patients described sharp, stabbing pain from the shoulder down to the arm, forearm and fingers, most of them also experienced a dull, gnawing ache, more or less constant, in certain parts of the extremity The pain either gradually progressed downward to the distal parts of the extremity, beginning in the shoulder blade, or was present in the entire area of distribution from the start Discomfort in the lower cervical region as an initial symptom was mentioned only infrequently Paresthesias involved the fingers chiefly, and in a few instances the whole extremity or part of the arm as well Coughing, sneezing and straining precipitated or aggravated the pain and paresthesias In the majority of cases certain movements of the neck had the same effect The type of the aggravating movements was not uniform

The distribution of the pain and paresthesias in the arm and forearm seemed to form a characteristic pattern according to the level of the lesion, in the fingers it is variable Lesions at the fifth cervical interspace with compression of the sixth cervical nerve root involved the anterolateral portion of the upper arm, the antecubital region and the radial aspect of the forearm, thumb or thumb and index finger, or the fingers might be spared, lesions at the sixth cervical interspace (seventh cervical nerve root) involved the posterolateral aspect of the upper arm, the olecranon and the dorsal aspect of the forearm, wrist, second finger, second and third fingers, or second, third and fourth fingers and all the finger tips In 1 case all the fingers seemed to be affected first, later the index finger alone was affected The patient with a rupture at the seventh cervical interspace (eighth cervical nerve root) had pain and paresthesias in the inner aspect of the upper arm and forearm and the little finger The shoulder blade was implicated in all instances regardless of the level of the lesion In 3 cases a burning pain was experienced in the leg on the side opposite that of the shoulder-arm syndrome Weakness of the arm or of specific muscles, as well as fasciculations and atrophy, was reported frequently In all but 1 case one or two major, and probably significant, injuries had been received some time prior to the onset of the disability

The more common clinical signs were (1) absence of cervical lordosis, (2) tilting of the head to the side opposite the lesion, (3) aggravation of symptoms by certain movements of the neck, (4) tenderness of the shoulder blade, supraclavicular area and lower cervical portion of the spine, (5) sensory disturbances in a "dermatome" distribution, (6) atrophy, fasciculations and weakness of certain muscles, (7) diminished arm reflexes on the side of the lesion, and (8) more active leg reflexes on the same side



None of the patients presented all these changes. Electromyographic studies were made by Dr Arthur Watkins and Dr Mary Brazier in 10 cases. Compression of the seventh cervical nerve root produced spontaneous discharges most often from the triceps muscle, as well as from the deltoid, extensor carpi ulnaris, extensor carpi radialis, flexor carpi radialis and opponens pollicis muscles. Recently it was observed that the intensity of the discharge varied with different positions of the neck. The cerebrospinal fluid protein was definitely increased in 7 cases, normal in 7 cases and nearly normal in 4 cases. The lowest value, 18 mg per hundred cubic centimeters, was found in the case with the largest disk fragment in the series. The dynamics were normal except in a case in which the patient was admitted with a history of long-standing pain in the shoulder and arm and recent paraplegia following a dental operation. Roentgenograms showed absence of cervical lordosis, degenerative changes in the lower cervical portion of the spine and narrowing of the fifth and sixth cervical interspaces. The narrowing of the interspace did not always correspond with the level of the lesion. Myelographic studies were performed in 17 cases. In 2 cases the oil could not be removed from the site of the injection. In the others a definite filling defect or arrest of the radiopaque medium was shown at the site of the ruptured disk. The contrast substance was removed according to the method of Kubik and Hampton.

In the majority of cases treatment had been previously carried out for such conditions as bursitis, neuritis, myofibrositis, arthritis and disease of the coronary arteries. Differentiation of the root compression syndrome and these entities is not usually difficult. As to the scalenus anticus syndrome, it is probably true that a ruptured cervical disk may produce spasm of the scalenus anticus muscle. There also may be relief of symptoms following section of this muscle, just as nonspecific surgical measures apparently were successfully used in the past for the treatment of ruptured lumbar disk. In certain instances the clinical differentiation of intraspinal root compression and extraspinal disease of certain components of the brachial plexus, of mechanical origin, will remain a difficult problem. However, ordinarily the combination of symptoms and signs in a case of ruptured cervical disk is such that extraspinal disease can be well ruled out. In doubtful cases myelographic studies will settle the question.

#### DISCUSSION

COL WILLIAM P VAN WAGENEN, M C, A U S. This is a fascinating subject. Major Scoville has been more interested in this phase of the problem than I. He has seen almost all the patients at the Army hospital at which we are stationed.

I wish the authors would comment further on the differential diagnosis of the ruptured cervical disk, particularly with reference to the scalenus anticus syndrome.

What percentage of civilians with pain in the shoulder and pain radiating down the arm actually have ruptured cervical disks? In the Army it is very small. The number of cases of ruptured disk in persons of military age is not great. I suspect that the authors' patients are older, it would be interesting to know what age group they represent. There is a great deal of variation in the distribution of pain referable to the cervical nerve roots. My colleagues and I see that every day. The variations in the arrangement of the brachial plexus are enormous.

A comment by the authors on the surgical details of their approach and treatment would be of interest.

This study has been carefully carried out, and it has been a pleasure to listen to its presentation.

MAJOR WILLIAM B SCOVILLE, M C, A U S. I have been interested in this clinical entity since 1939, and with Colonel Spurling I published a report of the surgical treatment in 12 cases in 1943 (*Surg, Gynec & Obst* 78:350 [April] 1944). I am in accord with Colonel Van Wagenen's statement that a cervical

ruptured disk is a rare surgical lesion, but I believe that it is a common clinical entity. In other words, the disability is mild and only occasionally warrants surgical intervention. Compression of the nerve roots at the lower cervical vertebral foramina accounts for most of the diagnoses of scalenus anticus syndrome, brachial neuralgia and other obscure neuralgic pains of the shoulder and arm. When roentgenograms reveal arthritic changes localized to one interspace, I believe that the probable diagnosis is a cervical ruptured disk rather than hypertrophic arthritis. The so-called hard disk is three times as common as the soft variety in the cervical region. The hard variety is characterized by absorption of the nucleus with narrowing of the interspace, localized bony proliferation into the intervertebral foramen and a hard transverse ridge formed by protrusion of the cartilaginous plate and concomitant changes in the bone.

The proportion of clinical cervical ruptured disks requiring operation is low—probably less than 10 per cent. In the authors' series it constituted 6 out of 40 cases. In the remainder of the cases the disability was mild. The ratio of operations for ruptured cervical disk to operations for ruptured lumbar disk ranges from 1/50 to 1/12, being 6/270 in the authors' series, 2/120 at Cushing General Hospital and 12/145 at the Walter Reed General Hospital.

**Diagnosis.** In all cases in the authors' series, the lesion was located in the fifth or the sixth interspace. The signs and symptoms include stiffness of the neck, pain in the shoulder, radiating down the arm to the thumb and forefinger, weakness of grip and of function of the triceps and biceps, with corresponding loss of reflexes, subjective numbness of the index finger or the thumb, positive reaction to the neck compression test, tenderness over the adjacent spinous process, and increase of pain on coughing and sneezing. Vasomotor signs and ulnar distribution of the pain favor a diagnosis of scalenus anticus syndrome. As pointed out by Michelsen and by Spurling and Scoville, spasm of the scalenus muscle may be a prelude to cervical ruptured disk, but the pain soon shifts from an ulnar to a radial nerve distribution.

**Myelographic examination,** using 6 cc of Pantopaque (iodized poppyseed oil, with special cohesive properties) and then removing it, should be done in all operative cases. A single Bucky film is generally sufficient to show the entire lower cervical dura and root sleeves. Roentgenographic diagnosis of a cervical ruptured disk is made on the basis of (a) narrowing of the intervertebral space, (b) bony proliferation into the intervertebral foramen in oblique views and (c) a lateral dural defect or obliteration of a root sleeve in the myelogram. I have seen 2 cases of combined rupture of cervical and lumbar vertebral disk in which classic defects were revealed in the myelogram.

**Operative Approach.** I strongly advocate the upright "cerebellar" position. A buttonhole unilateral approach, with laminotomy, similar to the lumbar approach, is used. The hole through the overlapping laminae can best be made with a high speed spherical drill, followed by chisel and curet. The dural root sleeve comes off at right angles to the dura, in contrast to the lumbar root sleeves. This prevents displacement of the dural sleeve during removal of the ruptured disk. The cervical intervertebral space is too narrow to permit insertion of pituitary rongeurs. The best that can be done is (a) to remove any "soft" fragments of a protruded nucleus (rare), (b) curet the interspace with a small curet (difficult), (c) remove with curet, nail punch or dental chisel, any cartilaginous ridge (beware of stimulating further proliferation of bone), and, lastly, (d) cut the sensory root (three fourths of the total diameter of the root) and occasionally transplant the motor portion of the root in a cephalad direction by slitting the dura upward. This was done in 5 cases, with improvement in motor (triceps) function and no appreciable sensory loss.

I wish to congratulate Dr. Michelsen on his excellent survey, I believe his operative series constitutes one of the largest in the United States.

MAJOR F. H. LEWEY, M. C., A. U. S. Rupture of the intervertebral disk seems to occur as a result of infraction of the epiphysial plate of the upper and lower

adjacent vertebrae, subsequent slipping of the disk and eventual biting off of its protruded part by the sharp edges of the vertebrae in a sudden dorsiflexion of the spine. The possibility of an epiphysial infraction is facilitated by the persistence of a certain stage of normal embryonic development in many normal persons.

**DR SAMUEL LOWIS** A patient with rupture of a disk of recent traumatic origin at the fourth cervical interspace, with compression of the fifth cervical root, showed the following signs: diminution of the biceps reflex, pain extending into the anterior aspect of the forearm on the lateral side and into the medial side of the axilla, an area of diminished sensation on the anterior surface of the upper arm adjacent to the axilla and another area of diminished sensation at the base of the thumb, with no signs or other symptoms referable to the hand or fingers, and pain and tenderness in the interscapular and suprascapular areas.

**DR JOSEPH F DORSEY** I should like to ask Dr Michelsen whether one should obtain a myelogram in all cases of ruptured cervical disk. Roentgenograms of the cervical portion of the spine show narrowing at the affected interspace. In addition, the level may be localized precisely by neurologic examination. When a hemilaminectomy is done, two roots are usually visualized, so that the chance of an error in the level of the operative site is minimal. To me it would seem that myelography is an unnecessary procedure.

**DR JOST J MICHELSEN** The average age of our patients was 45, the youngest being 32 and the oldest 68. Differential diagnosis of the scalenus anticus syndrome and root compression may be difficult indeed. However, the sensory manifestations of root compression have a different distribution. Only with lesions at the seventh interspace may they resemble those of neuritis of the lower part of the brachial plexus, of mechanical origin. The postural factors are different, too. Aggravation by certain movements of the neck, as well as by coughing and sneezing, is suggestive of an intraspinal lesion, certain movements which relieve the discomfort in cases of ruptured disk aggravate pain and paresthesias in cases of a spastic scalenus anticus muscle. Changes in the blood pressure and pulse, which are common with, and diagnostic of, compression of the brachial plexus, are absent with ruptured disk. Injection of procaine into the scalenus anticus muscle may be helpful. Myelographic studies in doubtful cases will usually determine the site of the lesion when other methods fail. As to the surgical procedure, Major Scoville has answered some of the questions. We have not had any difficulty in using the ordinary instruments for laminectomy, namely, the duck bill rongeur, the Kerrison rongeur and, occasionally, a small chisel and hammer. The ruptured disk was removed either extradurally or intradurally. In all the cases in which operation was performed free fragments of cartilage were lifted out with a forceps, without dissection or curettage. I have omitted another case in which there were exostoses, which Major Scoville mentioned. In 1 of our cases the posterior root was sectioned after removal of the fragment of disk. All the patients recovered after the operation, only 1 recurrence has so far been observed. Myelographic studies were performed for several reasons. It was felt that the presumptive diagnosis of this relatively new entity should be confirmed by unequivocal evidence of the type, location and size of the lesion. We have not had much success with the neck compression test. Perhaps we did not use it correctly. If the reaction was positive, simple tilting of the head toward the side of the lesion precipitated or aggravated the discomfort, too. The indication for operation was based on the degree of disability. In all cases some type of conservative treatment had been given before the patients were sent to us, in 2 cases exploration was not done, since the discomfort was not severe enough to warrant operation.

**Effect of Anoxia as Measured with the Electroencephalogram and the Interaction Chronogram in Psychoneurotic Patients** DR JACOB E FINESINGER, DR ERICH LINDEMANN, DR MARY A B BRAZIER and DR ELIOT D CHAPPLE

This paper will be published in full in the *American Journal of Psychiatry*

Studies on the Physiology of Flight Effect of Anoxia on the Electroencephalogram of Psychoneurotic and Normal Adults DR MARY A B BRAZIER

In the field of electroencephalography, the crux of the problem can be expressed in the form of two questions (1) Where do the currents originate, and (2) What determines the frequency at which they oscillate? The answer to the first question is fairly well established, and it is generally recognized that the origin of the electrical potentials is in the cells of the cerebral cortex. The second question has not yet been fully answered, but a body of evidence is being collected to indicate that the rate of oscillation of these potentials is directly correlated with the rate of metabolism in the cells of the cerebral cortex. This evidence has accumulated from observations of the following type, if the metabolism of the cortex is upset by its being deprived of sufficient substrate, namely, glucose, the electroencephalogram will show slowing. If the metabolism of these cells is stimulated by some such agent as thyroxin or pyrexia, the electroencephalographic frequency again will speed up, or if the metabolism of these cells is depressed by depriving them of sufficient oxygen, the electroencephalogram, again, will reflect the change. The last situation, in which the electroencephalogram responds to anoxia, is the subject of this study.

Bergei was the first to show that lowering of the oxygen concentration of the inspired air slowed the rate of the cortical potentials, and this observation has since been abundantly confirmed by other investigators. It was the purpose in this study to apply this fact as an objective method for assessing the degree of response of a subject to low oxygen concentrations, and this entailed the development of a method of measurement of these rhythms in order to be able to quantitate any change which took place.

A tracing was shown of a normal electroencephalogram, taken while the subject was breathing air. Below it was the record of the same subject when breathing a mixture containing only 8.8 per cent oxygen (a mixture simulating an altitude of 20,000 feet [6,060 meters]). The slowing of the electroencephalographic rhythm was obvious to the naked eye, but in order to measure the exact degree of slowing, a method had been developed for quantitative analysis of these records.

A measuring rule, originally designed by Dr. Hallowell Davis, was used for this work. It consists of a transparent sheet marked off for the various frequencies; this sheet is laid over the electroencephalographic record so that the interval between peaks of the waves can be determined and their frequency read off from the figures at the side of the scale. In this way it is possible to determine the percentage of each record which is covered by waves of the various frequencies, and a distribution curve can be assembled representing the amount of each frequency present. An example of such an analysis was shown.

In the sample shown, the greater portion of the record consisted of waves of 10 cycles per second, with lesser amounts of other frequencies, so that the distribution curve of the frequencies showed a peak at 10 cycles. If any slowing of this electroencephalographic rhythm took place, owing to the subject's breathing air of low oxygen content, one would expect the whole distribution curve to move to the left, into the range of slower frequencies, and this, in fact, was what was observed.

A tracing was shown, which was for 1 subject only, with a solid line representing the distribution of frequencies in the electroencephalogram when air was breathed, and a broken line the distribution when the oxygen was reduced to 8.1 per cent (equivalent to an altitude of 22,000 feet [6,666 meters]). At the low oxygen level, the whole curve had shifted to the left, into the slower frequency range. There were many features of this shift which might be used as measurements. For example, the amount of activity slower than a certain frequency could be used, and this would obviously be greater in the left hand curve than in the right and would give some measure of the slowing of the electroencephalographic

potentials, or one could use the shift of the peak of the curve, which is called the dominant frequency, since that was the frequency which dominated the whole of the electroencephalographic tracing. For the purposes of simplicity and brevity, the latter feature was presented only in the data which follow.

In this subject's record the dominant frequency shifted by  $\frac{1}{2}$  a cycle when the oxygen was reduced. In any large group of subjects who are breathing air the dominant frequency varies from person to person, but when charted it shows a distribution curve around the most common value for normal people, which is 10 to 10.5 cycles per second.

Such a distribution curve was shown for 37 subjects breathing air, together with the shift for the same 37 subjects to slower frequencies at oxygen levels below 11 per cent (i.e., at simulated altitudes above 15,000 feet [4,545 meters]). The degree of this shift was statistically significant. This chart showed a difference between the electroencephalograms of a group of subjects breathing air and those of subjects at low oxygen levels, but it did not give information as to whether this slowing takes place suddenly at an altitude of, perhaps, 15,000 feet or whether it is a response which is correlated with the level of anoxia involved.

In a table, the same series of 37 subjects were divided into three portions: those at oxygen levels below 9 per cent (i.e., above 20,000 feet), those at oxygen levels between 9 and 10 per cent (18,000 to 20,000 feet [5,454 to 6,060 meters]), and those at oxygen levels between 10 and 11 per cent (15,000 to 18,000 feet). It is immediately clear that the average slowing was greater the lower the oxygen level. Here then, is one variable which affects the degree of slowing, in other words, the degree of slowing is dependent on the degree of anoxia. There is, however, another variable at work, the carbon dioxide level. Great technical difficulty was experienced in eliminating all the expired carbon dioxide from the circuit, since it accumulated so quickly and some inevitably remained to be rebreathed. In none of the 37 cases reported here was the inspired carbon dioxide over 0.5 per cent, but a striking difference was found in the degree of response to low oxygen levels between those subjects who were breathing less than 0.3 per cent carbon dioxide and those who were breathing between 0.3 and 0.5 per cent carbon dioxide. There was a greater slowing of the electroencephalogram at the lower carbon dioxide levels.

When both the oxygen and the carbon dioxide level were low, there was the greatest slowing of the electroencephalogram. When the oxygen was reduced only to the 10 to 11 per cent level and the carbon dioxide was over 0.3 per cent, the electroencephalogram showed no slowing. The influence of carbon dioxide on the reaction of subjects in low oxygen concentrations was expected from all the work that has been done in this field, but it was an unexpected result to find that carbon dioxide exerted its influence in such low concentrations as 0.3 per cent.

These two variables, the oxygen and the carbon dioxide level, were, however, not the only two variables in the present data. In the original group of subjects under discussion, there was a third variable, namely, that of this population 25 were psychoneurotic patients and 12 were normal adults. Since it was one of the objectives of this study to determine whether patients with psychoneuroses reacted to oxygen deprivation in the same way as normal subjects, the results have been analyzed from this point of view.

To simplify the issue, one variable was eliminated from this analysis, namely, the influence of carbon dioxide. Only those experiments in which the carbon dioxide was less than 0.3 per cent were included, hence, only 18 subjects were included. It was found that the electroencephalograms of the psychoneurotic patients showed a greater degree of slowing than did those of the normal adults. The difference found by measurement was of statistical significance. This finding that the psychoneurotic patients show a greater slowing of their electroencephalo-

graphic frequencies under anoxic conditions than do normal adults has many implications, especially if one goes back to the opening question raised in this paper, namely, that the frequency of electroencephalographic potentials reflects directly the condition of metabolism in the cortical cells. The electroencephalographic results suggest that the metabolism of the cortical cells of the psychoneurotic patients is more labile than that of normal adults.

DISCUSSION ON PAPERS BY DR FINESINGER AND ASSOCIATES AND DR BRAZIER

MAJOR F H LEWIS, M C, A U S This is a series of stimulating and interesting experiments and observations. I was specifically impressed by Dr Brazier's contribution, realizing how much more information can be derived from the electroencephalogram by application of statistical methods.

Did I understand Dr Finesinger correctly as stating that the changes of frequency of the electroencephalogram under his experimental conditions followed Arrhenius' equation? This would mean that the reaction time of the physicochemical processes underlying the electrical potentials of the electroencephalogram rises with the temperature but that the irregularity of this so-called coefficient of temperature followed Arrhenius' rather than van't Hoff's, equation. Was this statement meant to be an analogy, or did the group of patients with increased or decreased activity show changes in their temperature characteristics?

DR WILLIAM G LENNON I want to express my appreciation of this well integrated and well coordinated study. I hesitate to suggest additions to the already complicated observations, but I wish Dr Finesinger had made use of his technique for recording the pulmonary ventilation. Lack of oxygen induces increased respiration, which, in turn, sharply alters the carbon dioxide content of alveolar air and of arterial and cerebral capillary blood. Therefore I object to the title, which implies that observed changes in the electroencephalogram are due to anoxemia alone. Measurement of the small variations in the carbon dioxide content of inspired air can be of no significance, for the severe anoxemia induces hyperpnea, which greatly decreases the carbon dioxide content of arterial blood. The relative importance of oxygen and of carbon dioxide in altering the frequency of brain waves can be decided only by measuring the levels of these two gases in the blood entering and leaving the brain. Dr and Mrs Gibbs and I made observations of this sort after putting a needle into an internal jugular vein and another in a femoral artery. We found that carbon dioxide was more influential in altering brain wave frequencies than was oxygen. We could carry subjects to unconsciousness with anoxemia, but if we kept constant the levels of carbon dioxide in the arterial blood there was no appreciable slowing of brain waves. Dr Brazier suggested that unusual effects in neurotic patients may be due to something specific in the metabolism of the neurons of these patients. Possibly, however, such persons have an unusual respiratory response to anoxemia, which would cause unusual changes in the carbon dioxide content and in the brain waves. Again, their cerebral circulation might respond in an unusual way to a given change in the oxygen or the carbon dioxide level of the arterial blood. We observed that patients with petit mal had unusual slowing of brain waves with hyperpnea. We found that this slowing was due to failure of the cerebral arterioles to constrict with overventilation. Failure of constriction meant failure of slowing of the blood flow, and hence lowering of carbon dioxide tension in the capillaries and resultant slowing of the brain waves. Some such mechanism in neurotic patients would seem simpler than postulation of a cortical cell metabolism which is specific for neurotic persons.

LIEUT COL JACKSON M THOMAS, M C, A U S I am not qualified to comment on the oxygen and carbon dioxide factors studied in this investigation. As a clinical psychiatrist, however, I should like to know what sort of questions the patients were asked. What was the nature of the interviews? I wonder whether all the patients should be classified as psychoneurotic. The speaker's use of the words "activity" and "inactivity" in describing the patients puzzles me.

DR ERICH LINDEMANN In order to obtain a comparison of the clinical behavior of subjects during the experimental interviews, we obtained disk recordings of the verbal interaction between the patient and the interviewer. The changes in behavior noticeable were of two types. In one type the patients became restless, appeared distressed and demanded permission to leave the anoxia chamber—this was likely to happen during the mixing period. In the other type, the patient became increasingly uncommunicative and then ceased to respond altogether, so that the experiment had to be interrupted. These two extremes, acute apprehension with restlessness, on the one side, and apathy with failure to respond, on the other, seemed to be two poles of a continuous series presenting various combinations of the factors mentioned. It is of interest that the restless state was often attended by phenomena suggesting autonomic stimulation—sighing respiration, flushed face and profuse sweating—while the apathetic state seemed to progress insidiously without any such dramatic manifestations.

During the second interview, as the experiment proceeded, we again noticed two different states: one of overactivity, with somewhat garrulous talking with euphoria, the other of reduced communication, shorter responses, stereotyped answers and inaccurate answers. In addition, we noticed evidence of the disintegration of language, there were no complicated sentences and frequently only fragments of sentences, monosyllabic answers. There was also some dysarthria.

The complexities of the changes in the clinical behavior suggested that they involved not only the effect of anoxia on cortical functions but also effects on the autonomic nervous system, probably related to stimulation of the carotid sinus. In former work, Dr Finesinger and I were able to show that injections of epinephrine and mecholyl may be followed by pronounced changes in the rate of verbal activity of psychiatric patients during interviews, the former reducing and the latter increasing activity. It is likely that the changes in the rate and quality of verbal activity result from both factors, autonomic and cortical.

That autonomic stimulation may occur at smaller degrees of reduction in oxygen than interfere in cortical functions would explain why changes in rate of activity were observed at relatively high levels of oxygen, while changes in the electroencephalogram appeared only at more pronounced degrees of anoxia.

DR JACOB E. FINESINGER In reply to Colonel Thomas' question. The basis of our diagnosis was description of symptoms. The patient has disorders diagnosed as anxiety neurosis, hysteria, reactive depressions and combat neurosis—the kind of patient seen here today. We tried to control the topics in the interview. We tried to keep away from charged topics. We thought the school topic was probably not a charged topic for most people. We tried to standardize the interview as best we could, knowing that there were gaps. As to activity and inactivity, Dr Chapple will comment on that.

DR ELIOT D. CHAPPLE We mentioned the work of Stier and Pincus on respiration and activity in order to point out that some of the mechanisms of control activity were possibly located in the lower centers, not to imply that we were changing the temperature of our subjects in order to use the Arrhenius equation.

DR MARY A. B. BRAZIER In reply to Dr Lennox. It would add considerably to knowledge of the effect of anoxia on cerebral activity to have information from the blood stream, but in this particular experimental situation, in which we try to have as normal an interview as possible, such manipulation is out of the question. I agree that the data presented here are not critical in deciding the roles of oxygen and carbon dioxide, but such critical data do exist and have come from another laboratory. Since the originator of that work is here tonight, I shall ask him to answer that question.

DR HUDSON HOAGLAND, Worcester, Mass. The fact that brain wave frequencies may correlate better with the content of blood coming from the brain than they do with the corresponding oxygen content does not at all militate against the view of the importance of cell respiration as a determinant of brain wave frequencies.

There is a large factor of safety for oxygen transported to the brain, and hence oxygen tension can be considerably reduced without modifying cerebral respiration, since the limiting factor is the degree of saturation of enzymes and this is not affected until after considerable reduction in the oxygen content of the blood

It seems to me that there is one set of experiments which conclusively demonstrates that alpha frequencies are directly proportional to cerebral respiration. These experiments have been published in a series of papers by our group at Clark University since 1936 and were reviewed in 1944 (Hoagland, H. *Colloid Chemistry*, edited by J. Alexander, New York, Reinhold Publishing Corporation, 1944, vol 5). They show that the "energies of activation" of the processes determining alpha frequencies are identical with those found for certain specific key respiratory enzymes studied *in vitro* and known to be limiting factors in cerebral respiration. There is no way in which the results of these experiments can be interpreted except in terms of this view, namely, that the frequencies in resting subjects, with closed eyes, are directly proportional to the speed of certain chemical steps (specific enzyme pacemakers, or bottlenecks) in the sequence of cellular respiration. This view is consistent with our findings that dinitrophenol and thyroxin speed the rhythms and with our observations and those of other investigators showing that alpha frequencies are slowed by hypoglycemia.

According to my view, carbon dioxide as an acid metabolite produced by cellular respiration is an important agent in firing the cell. Its production in the cell is a direct determinant in the cell's recovery from its refractory phase, since it acts to determine potassium diffusion gradients, which are the basis of bioelectric potentials according to work from a number of laboratories. Thus the more carbon dioxide is produced the more rapid the recovery, and hence the faster the frequency of firing of the cells. This view is not inconsistent with what is known of the role of acetylcholine in relation to bioelectric potentials. Of course, the absolute frequency of firing of a chain of cells depends on the electrical constants of the tissues, as well as on respiration, but these electrical constants must average as stable values for any given group of cells, such as those contributing to the alpha rhythm in the resting subject with closed eyes. Otherwise, the results obtained in our measurements of energies of activation, previously referred to, relating alpha frequency to respiratory enzyme systems, would not have been obtainable.

There is, thus, no meaning to the controversy about oxygen versus carbon dioxide in relation to the dynamics of brain waves. Carbon dioxide produced at a rate proportional to the cell's respiration (respiratory quotient of the brain is unity) can fire the cell by creating potassium potentials. If this mechanism is correct, one should expect the results obtained by Gibbs and others, who have found that brain wave frequencies parallel more closely the carbon dioxide than the oxygen content of the blood when air containing varying amounts of carbon dioxide and oxygen is breathed.

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Madelaine R. Brown, M.D., *Presiding*

Regular Meeting, Oct 18, 1945

**A New Psychiatric Rating Scale** DR WILLIAM MALAMUD and DR HUDSON HOAGLAND, Worcester, Mass., and LIEUTENANT I CHARLES KAUFMAN, Medical Corps, Army of the United States

Quantitative rating of the degrees of intensity in the course of mental illness is of fundamental importance if changes in the behavior of patients with mental disease are to be correlated with physiologic and biochemical data.

Twenty items of significance in the evaluation of the status of psychotic patients were selected. These items were chosen on the basis of two factors



(a) items in which the degree of variation from the average or normal was meaningful, (b) items which could be observed and evaluated equally well by independent observers. The functions selected fell into three groups: (1) those that could be observed directly during an interview, (2) those that could be obtained through communication with the patient during an interview and (3) those aspects of behavior that could be observed by the ward personnel over a twenty-four hour period.

Numerical values were assigned to each of these items, describing their degree of departure from normal in a given case. The maximum departure for each function from the zero norm was 2 units, and thus the rating of an individual patient might range from zero to 40 units.

Three psychiatrists independently rated each of 20 schizophrenic patients interviewed by one psychiatrist in the presence of the other two, and each physician independently recorded his score. Correlation coefficients were then determined to test the scale. The scores of Dr. M. correlated with those of Dr. F., giving an  $r$  value of 0.907 ( $P < 0.01$ ), and Dr. M.'s scores correlated with those of Dr. K., giving an  $r$  value of 0.868 ( $P < 0.01$ ). It was found that instructed nurses can use the scale so as to give meaningful ratings of psychiatric status when compared with ratings given independently by a psychiatrist. The data indicate that the criteria underlying the ratings are sufficiently communicable and reproducible to make the scale practically serviceable in quantitating the over-all degree of the psychotic state.

#### DISCUSSION

DR. FREDERICK L. WELLS. It is obvious that these presentations open an enormous field of discussion. It is only from one point of view that it would be pertinent for me to speak, that is with regard to Dr. Malamud's rating scale. When one has been in this field for a number of years, one becomes imbued with the historical point of view. I never like to miss saying a word for my old teacher, Dr. James McKeen Cattell, who really started this sort of thing; he had the whole rating scale idea developed in the early 1900's. Then, curiously, it dropped out of sight. Twenty years later it reappeared. Textbooks make little reference to Cattell in the matter. The multidimensional approach has been made explicit under the name of *Gestalt*. Since the days of early Greek philosophers, it has been known that the whole is greater than the sum of its parts. When the scale was put on the screen, I thought that we were going to see how these specific traits show up and how people agree with respect, for example, to memory or sex responses, what we actually have is a presentation based on the summated score of all these traits. A group of clinical psychologists would want to know the agreement with regard to the specific traits of the scale, and they would question whether these various traits arrange themselves in a linear scale quite as effectively as they should for a rating on specific traits. One is faced with the question, "How much does this scale add to what would be learned if the psychiatrist asked, 'How well is this patient?'" Is not the result the same except that the conclusion is arrived at by a summation of traits rather than by a single one? Such rating scales have been used at Worcester before. I recall some rather elaborate procedures of the sort in Dr. Hoskins' research on dementia praecox. To come back to the statistical point of view, it is interesting to compare this scale with other attempts of the same kind. When Dr. James S. Plant and I were at McLean Hospital, we discussed the possibility of constructing such a scale, and he published the method in the *American Journal of Psychiatry* in 1922.

With regard to global traits, these traits have to be broken down. Take memory, for example. Memory is a function made up of many components. I wonder how justified one is in lumping a number of traits like these. Wechsler has brought out a memory scale. He has pointed out that I was the first person to use the term "memory quotient", I fear it would be better for psychological discipline if I had also been the last.

Dr Malamud's point is well taken—that one cannot get a satisfactory picture of a patient, and certainly not of a normal person, with rating scales, but that one has to have rating scales for purposes of comparison. Psychologists use them too much in evaluation of personality when they have no contact with the actual person, they are simply numbers attached to trait names. Statistically, it seems valid, but as soon as one has to square the rating scale with a fair psychiatric evaluation of personality, there is trouble. A rating of this type cannot tell anything like the whole truth about the patient. Ultimately one needs another sort of multidimensional approach—from various levels. One can well start with the fundamental concepts of Edward J. Kempf and work through Sheldon's ideas on "temperament," though with no commitments on the somatic side. A next step is through the penetrating scheme of personality traits developed by Henry A. Murray.

I should like to ask one question with respect to the history of these patients. Has there been any observation of their prepsychotic personalities?

DR FREDERICK WYATT. Dr Malamud, in his interesting report, has touched on some of the difficulties of his experiment. In his attempt to rate behavior, his predicament is familiar to the psychologist. We psychologists are constantly under pressure to achieve standards of quantitative exactness in our work such as the natural scientists keep dangling before our eyes. We have certainly tried hard. I wonder, however, whether in psychologic and psychiatric work we are not dealing with a material which *a priori* does not lend itself to the methods of some of the natural sciences. It has yet to be shown that the standards and methods specific for them are necessarily binding for all scientific endeavors.

Three problems have always been encountered with rating scales. 1. Which traits or modes of behavior should be selected as the important ones? 2. How can these observations be transformed into quantities? 3. What will the measure of quantification be, or what set of data will supply the standards against which the individual case is held and rated as high or low? With regard to the first two questions, I could grasp only a few of the variables shown on the slide. In one of them, homosexual and masturbatory behavior seemed to be to the right of the middle line, while sexual behavior and exhibitionism were to the left. So far as present knowledge goes, each of these forms of sexual behavior is quite complex in itself, as is their dynamic basis. On the quantitative basis proposed, twice the rating for homosexuality would equal the rating for exhibitionism. I am quite aware that Dr Malamud and his associates had nothing of this kind in mind. Yet the reduction to absurdity may show the difficulties inherent in the transmutation of complex behavior patterns into additive quantities.

Now to the third point. What standards should the rating follow? The problem has two sides. One is the consistency of the observer in his own rating, the other is the position of the subject with regard to the features of the rating scale and involves the question of the uniformity of the population. In our work, my colleagues and I deal with a great variety of people. What does "premorbid personality" mean in the sense used here? Prior to his psychotic breakdown, a patient may have had marked homosexual tendencies, yet they may not have interfered with his general adjustment. The consistency of the rating observer seems to me to offer the gravest problem. How can he know whether he should rate the first members of his population high or low when only a larger group will indicate representative trends and changes. His idea of an average value for any of the qualities in the group shifts with the number of people whom he is seeing—often unnoticeably so. Under these conditions, he can never be quite certain whether he is consistent in his rating from one member of the population to the next. Furthermore, the psychiatrist is likely to rate a patient differently in the light of what he has learned about him during several months of observation.

Of the desirability of a rating scale such as the one presented here there is no question. A more extensive scale was published some time ago in the

*Journal of Abnormal and Social Psychology* Dr Malamud's scale has the advantage of being more concise. I should like to mention the rating of personality traits and behavior in a recent study at the Harvard Psychological Clinic in which I participated. First, the traits of each subject were rated by a group of observers individually and were unified only after contradictions in rating had been discussed and clarified.

DR ROY G. HOSKINS The question of other rating scales has been raised. Our previous experiences at Worcester have been numerous and have entailed the many perplexities that the discussers know are there. Twelve or fifteen years ago, my colleagues and I studied the Kempf scales, as used at the Phipps Clinic, the Plant scale, and various others. Then we selected about one hundred and forty traits and had four psychiatrists apply the rating scale for those traits to a group of patients. As standards we selected patients who were fairly representative and in a stable condition. Some of the traits failed to correlate with anything significant. The number of traits was ultimately reduced to about forty, which correlated rather well. At that point we realized that we must either have more psychiatrists or work only on rating scales, we decided, therefore, to go on with other activities and left the matter in abeyance. The crux of any of these systems is the weighting, as Dr Wells suggested. It is possible that ten traits properly selected and weighted would be quite as adequate as any larger number. Dr Wells asked how our simple over-all five point rating system worked. It proved to be fairly satisfactory. Perhaps the chief advantage of a composite scale is the confidence that is afforded the psychiatrist in his over-all judgment. One's thoughts go to Mephistopheles and the student "How comforting it is to have so many things in one's notebook." Actually, the combined judgment of the psychiatrists as to the degree of severity of the psychosis at any given time correlated about as well as in any other system we have used. Dr Malamud informs me that the traits selected for his new scale are actually those which he has long used in making clinical appraisals of the psychosis in connection with which it was employed. The result, no doubt, is a schema that would function adequately in a service managed by Dr Malamud. Some other man in some other service might do better with a scale of his own devising.

DR WILLIAM MALAMUD I am grateful to the discussants for their interest in this method of approach and their helpful criticisms. Dr Wells and Dr Wyatt discussed the rating scale along rather similar lines. Dr Wells reminded us of previous attempts to construct rating scales, I wish to assure him that we were aware of these and have taken them into consideration. The only reason we speak of the present scale as "new" is that it is specially applicable in correlating psychiatric findings with special types of physiologic data.

Dr Wyatt asked whether the rating scale was devised as an attempt to compensate for a feeling of inferiority in relation to the exact sciences. Certainly not! It was, I should say, an attempt to adjust ourselves to a group with whom we were working but who expressed themselves in a manner different from ours. In our clinical work and in our evaluation of the condition of our patients from day to day, we have always made use of some form of quantitative measure. Otherwise, we could not speak of relative degrees of seriousness of the patients' maladjustments. The present scale is simply a translation of this method of evaluation into terms which lend themselves to correlation with physiologic data.

The question was asked as to our standards of comparison. So far as possible, we try to use as a base line the behavior of the patient prior to his disease. Obviously, we have to rely mostly on the history as obtained from the relatives. Here, again, we have followed established clinical procedure. When a patient's condition is evaluated, we ask ourselves, "In what way is his present behavior different from that which people usually expected of him?" The "usually expected" is what we take as the average, or C, level, and the deviations are judged in relation to this norm.

Dr Wyatt wishes to know whether the psychiatrist's ability to use the scale does not improve with experience. Obviously it does. This is true of the use of any method of evaluation. However, the difference is not quite so great as might appear likely. Thus comparison of the results of my rating and those of Dr Kaufman's showed little discrepancy, whereas there is considerable difference in the number of years the two of us have worked in this field. The important factor is that the items rated are in the main objective and are therefore not particularly dependent on personal impression. If a person is mute or refuses to eat or is untidy about his personal appearance, there really is not much room for differences in recording such a fact. Similarly, if the patient states that he is sad or angry, it does not matter how experienced the person is who records such a statement. The scale, however, is particularly useful for the day by day rating of a patient by the same physician. Under such conditions, the differences can indicate only changes in the patient's condition.

Dr Wells's question concerning the prepsychotic personality of persons with involutional psychosis will perhaps take us too far afield. I refer him to the work of H. D. Palmer and to our own previous publication (Malamud, W., Sands, S. L., and Malamud, I. *Psychosom Med* 3:410, [Oct] 1941).

**Changes in the Electroencephalogram and in the Excretion of 17-Keto Steroids Accompanying Electroshock Therapy of Agitated Depression.** DR HUDSON HOAGLAND and DR WILLIAM MALAMUD, Worcester, Mass., LIEUTENANT I CHARLES KAUFMAN, Medical Corps, Army of the United States, and DR GREGORY PINCUS, Worcester, Mass.

The psychiatric rating scale discussed in the preceding article was used in the study of 13 women with agitated depression. Ratings were made not less than three times a week—before, during and after periods of eight to fifteen electroshock treatments. Electroencephalograms were recorded over these same periods twice a week. During the treatment period (two shocks per week) the electroencephalograms were taken on the day following that of shock treatment. Samples of urine were also collected from time to time during the pretreatment, treatment and post-treatment periods.

The psychiatric ratings were found to correlate well with fast (greater than 13 per second) frequencies in the electroencephalograms. When the patient improved, the percentage of time these waves were present was reduced. However, there was also a tendency for the fast waves to return in some patients showing good remission.

The diurnal rhythm of the morning rate of 17-keto steroid excretion divided by the night rate was calculated as a measure of adrenal cortical activity. While in normal persons this value is 1.60, in the patients studied the mean pretreatment value was 1.03, during treatment the mean value rose to 1.32 and in the post-treatment period it declined to 1.25.

The possible significance of these findings was discussed in terms of questions they raise for future exploration.

#### DISCUSSION

DR ROBERT SCHWAB. In a recent paper (*Am J Psychiat* 102:49 [July] 1945) Bagchi, Howell and Schindler described the electroencephalogram before and after electric shock. They pointed out that it was a long time before the electroencephalogram returned to normal after shock treatments. The delay was related to the number and severity of the shock treatments. I agree that it is important to correlate certain changes in a particular part of the brain wave spectrum with clinical findings before and after shock therapy, but it is equally important to keep an eye on the total brain wave picture. I should like to ask Dr Hoagland how much time elapsed after the shock before the electroencephalographic records were obtained. It is well known that after electric shock convulsions or, indeed, after ordinary convulsions, the equilibrium of the electroencephalogram is disturbed for several days. I feel uneasy in

attaching much importance to small changes, particularly the faster frequencies, found during that period of cerebral electric instability

It has long been a temptation to physicians, particularly to psychiatrists, to have a rating scale of clinical symptoms and disabilities on a numerical basis comparable in simplicity to those used by ophthalmologists in rating visual acuity. I utilized such a scale in my psychiatric work overseas during the past two years, but most of my psychiatric colleagues were rather contemptuous of anything so simple. It is important, in my estimation, that efforts of this sort be extended and encouraged, as something may ultimately be worked out that will satisfy psychiatrists, laboratory workers and general practitioners

DR RUDOLPH NEUSTADT. In 1941 my colleagues and I studied a group of 11 patients before and after electric shock therapy with respect to changes in their blood chemistry. There were no changes in the hemoglobin content or in the white or the red cell count. Changes in cholesterol were inconclusive, as some patients showed an increase and others a decrease after treatment. In some patients the blood sugar increased after each shock treatment but returned to normal within a day. In all patients the blood creatinine showed a slight increase after each shock but returned to normal within twenty-four hours. All patients showed a decrease in the 17-keto steroid excretion of 50 to 70 per cent from the pretreatment level, and it required eight to ten weeks for the output to return to the previous level. There also was a striking reduction of creatinine in the urine. These findings indicate that electric shock treatment puts a great stress on the endocrine system, particularly the adrenal cortex. It takes a long time to recover from the effects of electric shock treatment. I cannot see how these figures compare with Dr Hoagland's, however, it is possible that the balance between day and night excretion of ketosteroids is already restored at a time when the excretion of total ketosteroids is still lowered.

DR HUDSON HOAGLAND, Worcester, Mass. I mentioned that our results, together with other, earlier evidence in the literature, indicated dramatic changes in the electroencephalogram following electroshock treatment in some patients. These changes usually take some time to subside when the series of treatments is over. They consist of slowing and increased amplitude of frequencies of less than 12 per second. But these effects do not correlate with directional changes in the psychiatric state. As I said, our records were always taken on days between shocks and were always spaced so as to occur either one day, for certain patients, or two days, for others, after shock. Two shocks were given and two electroencephalograms were obtained per patient each week, and the changes in the components of more than 13 cycles per second usually showed pronounced differences in a given patient between times when she was ill and times when she was well. Each patient was thus her own control. Twenty-five fold variations, from 50 to 2 per cent, in the amount of time the fast frequencies were present were not unusual, and these were very real changes. Because the amplitudes in this frequency range are low and the waves are irregular, the changes were not especially striking on casual inspection of the record. In instances of psychiatric relapse during the course of shock treatments, our figures indicate that these frequencies again come to occupy an increasing percentage of the record, and this fact militates against the view that they are products of the treatment per se, since the treatment is continuing routinely. The point is that our figures show a parallelism of the frequencies greater than 13 cycles per second with the psychiatric state.

I should like to ask Dr Pincus to answer Dr Neustadt's question.

DR GREGORY PINCUS, Worcester, Mass. Our data are not very decisive. Before shock treatment there appears to be great variability in the absolute levels

of 17-keto steroids excreted. In a number of women we found much higher levels than one would expect for persons of that age and sex. The output varied a great deal. The only thing that showed consistency was the sleep waking ratio, which was 1 or slightly above or slightly below. In some patients the absolute level fell after shock treatment. That is about all I can say on that point, and I think that the explanation offered may not be the only one. It does not necessarily follow that the shock treatment has lowered the output level. At certain ages one might expect a lower level anyway.

### Relation of Changes in Carbohydrate Metabolism and Psychotic States

DR HARRY FREEMAN and DR RALPH N. ZABARENKO, Worcester, Mass

A study was made of the relation of the dextrose tolerance and the psychiatric state in 28 acutely psychotic patients who were receiving electric shock therapy. The patients included 11 men and 17 women. Their average age was 30. Sixteen of the subjects had schizophrenia, while the disturbances of the others had been diagnosed as involutional melancholia, bromide intoxication, psychoneurosis and manic-depressive psychosis. Dextrose tolerance tests (Eaton-Rose technic) were made before shock therapy was instituted and at monthly periods thereafter for an average of six months.

Before treatment was begun, the dextrose tolerance of almost all the patients was grossly abnormal. There was a diabetic-like trend, indicative of a reduction in the ability to utilize dextrose. After treatment was finished, there were pronounced psychiatric improvement in 9 patients, moderate improvement in 12 patients, and no change in the other 7 patients. The dextrose tolerance obtained on the last occasion that the patient was seen was compared with values obtained before therapy was instituted. The patients were divided into three groups, depending on the degree of improvement, and mean values were obtained for each group before and after treatment. The data showed a tendency to lessening of the abnormality in the dextrose tolerance as a result of treatment in the group showing pronounced improvement, but the change was not significant.

Analysis of the individual cases showed a fairly good relation between the psychiatric observations and the type of dextrose tolerance obtained and indicated the reason for the lack of significance of the change in the mean values. In some patients a good social adjustment was made after treatment, and the dextrose tolerance became normal. In others the psychotic behavior disappeared but residual symptoms of anxiety and guilt feelings remained, and in such patients the dextrose tolerance remained abnormal.

It was the feeling of the authors that the abnormality in the dextrose tolerance depends primarily on the amount of emotional tension present in the patient, not on the psychopathic character of the behavior. It follows, therefore, that the sugar tolerance would become normal only when patients had sufficient insight into their problems so that they could deal with them in adequate fashion.

### DISCUSSION

DR ROY G. HOSKINS. Dr Freeman has treated with a light touch a situation which my associates and I have faced for several years. We have been interested in the blood sugar in schizophrenia for a long time. Our interest was intensified when the war started and we worked with military patients, of whom we have had about 200. For about 70 per cent of these patients who came into the hospital with mental disturbances an apparently "diabetic" sugar curve was obtained, while comparable values were found in only about 30 per cent of normal control cases. Dr Freeman has made many attempts to find out what the aberration means, what it correlates with. As he suggested, the correlation with anxiety is the most promising explanation, irrespective of the diagnosis the patient carries. That, however, is an unsatisfactory point at

which to leave the matter. One cannot explain a physiologic phenomenon by attaching a label to it. What is there about anxiety that leads to this aberration in the sugar curve? There are several possibilities. One is an interference with the normal insulin reaction. The level of adrenal cortical secretions might also be important. The thought that has been engaging my mind most recently is this. In a normal person the first provocative dose mobilizes the forces that handle sugar so that the second dose can promptly be dealt with and the sugar curve go no higher. It would seem that in schizophrenia the mechanism that normally takes care of the sugar is sluggish. Later it comes into function. A study of the reasons for this lag in the adaptation to hyperglycemia seems to offer the most promising point of attack.

DR HARRY C SOLOMON. Are these curves for acute psychotic subjects, and are the curves similar after several years of hospitalization?

DR J FOLCH. It is recognized that the central nervous system does not need insulin to handle sugar. In this test the central nervous system is acting on the system, not vice versa. It seems to me that the importance of this test would lie precisely in its being able to detect schizophrenia which would not be diagnosed by standard psychiatric examinations.

DR RUDOLPH NEUSTADT. Spelberg and Leff examined some 30,000 inductees for glycosuria and found only 19 cases, but in 10 of these 19 cases an abnormal result in the Exton-Rose test was followed the next day by a normal sugar tolerance curve with the standard three hour test. This raises the question whether the Exton-Rose test, as applied by Dr Freeman, is reliable enough for investigative purposes.

Dr Freeman is right in being conservative in his conclusions. There was a correlation between the sugar tolerance and the mental status in the depressed patients, but there was no correlation in his schizophrenic patients. Some of the latter showed normal sugar tolerance curves before treatment and abnormal curves after treatment in spite of clinical improvement. These findings seem to me to be characteristic of schizophrenia. My colleagues and I have studied the carbohydrate metabolism (sugar, pyruvic acid and lactic acid in arterial and venous blood) for several years. We have found changes from normal to abnormal and vice versa from one day to the next without any obvious physical or mental changes in the condition of the patients. The only definite finding is that schizophrenic patients are entirely unreliable. This is in marked contrast to patients with manic-depressive psychosis.

Did those patients who had an abnormal sugar tolerance before treatment show any clinical symptoms of endocrine abnormalities?

DR CLEMENS BENDA, Wrentham, Mass. I am surprised that Dr Freeman found only an increased sugar tolerance in his patients. I should like, therefore, to ask several questions. Several years ago Dr Bixby and I published a paper on sugar tolerance tests in which we included observations on the Exton-Rose dextrose tolerance of patients with mongolism. We tried to adjust the doses of sugar according to the weight of the patient, I wonder whether Dr Freeman did the same or used one standard dose for all patients. I wonder, also, whether any insulin tolerance tests were made on the same patients. Increased sugar tolerance is especially frequent with conditions associated with hypothyroidism. Were any cholesterol determinations or metabolism tests made on the same patients which would suggest hypothyroidism? Patients with anxiety are usually restless and overactive. Did Dr Freeman find any instance of decreased sugar tolerance?

DR ROBERT SCHWAB. In our work with chronic seasickness at the Naval Hospital here, three years ago, my colleagues and I found that subjects who were made sick on our "swing" had during this period an altered sugar tolerance curve so that the blood sugar hardly rose above normal. With the use of barium sulfate mixed with a dextrose meal, we proved that this was due to gastric stasis, the sugar mixture remaining in the stomach, blocked by the spasm of the pylorus produced by the motion sickness syndrome.

I wonder whether the reverse could occur in Dr Freeman's patients. Could the dextrose leave the stomach more rapidly than it would in normal subjects and hence give a diabetic appearance to the curve? Did Dr Freeman use barium sulfate with his dextrose mixture to ascertain whether this was so?

DR HARRY FREEMAN, Worcester, Mass. These dextrose tolerance curves were studied on acutely psychotic patients in the main. We have studied various types of patients, both psychotic and nonpsychotic, and have found that 70 per cent show abnormal trends, irrespective of the diagnostic subtype. It is our impression that the tolerance becomes increasingly abnormal as the emotional disturbance in the patient becomes more severe.

The accuracy of the Exton-Rose procedure in the diagnosis of diabetes is as high as that of the standard single dose procedure. The consistency of the two types of test is equally good, according to our own studies on nondiabetic subjects.

There is little value in adjusting the dose of dextrose to the weight of the subject. Studies in the literature show that after a minimum dose of dextrose is ingested, about 50 Gm, further increases have no effect on the height of the curve, although they do tend to prolong the duration of the hyperglycemia.

Insulin tolerance tests were made on about 90 patients. On the whole, the patients, irrespective of diagnostic subtypes, tended to show some resistance to insulin, 45 per cent of them showed a lesser fall in blood sugar than does any normal subject. However, there was no statistically significant relationship between the dextrose and the insulin tolerance of any given subject.

The thyroid gland does not play much of a role in the production of these abnormally high curves. Of the thyroid disorders, only hyperthyroidism produces a low tolerance similar to that found in these patients. However, our patients tended on the whole to have low basal metabolic rates, which one would expect to result in flat tolerance curves.

The problem of the absorption of the dextrose from the gastrointestinal tract is an important one. It would be expected that such high blood sugar values as we have found would result from excessively rapid rates of absorption. Studies on schizophrenic patients show that the rate of progress of a barium sulfate meal through the gastrointestinal tract is either normal or delayed. Furthermore, as another method of testing rates of absorption, we studied the absorption of xylose, a nonutilizable sugar, in patients with normal and with abnormal dextrose tolerance. There was no difference between the two groups, so it does not seem that varying rates of absorption account for the abnormalities in the dextrose tolerance values.

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## CHICAGO NEUROLOGICAL SOCIETY

Ben W. Lichtenstein, M.D., *President, in the Chair*

*Regular Meeting, Jan 8, 1946*

**Neuropsychiatry in the Mediterranean Theater of War** DR BENJAMIN BOSHES

**Compound Spinal Injuries Report of Two Cases** DR MILTON TINSLEY

Twenty-two cases of compound spinal wounds were analyzed, in 19 of which complete paralysis immediately followed injury. In all these cases early laminectomy was done. In 2 cases there was remarkable return of function, and these cases were reported in detail. In this series there was only 1 death and no post-operative infection.

Roentgenographic examination was found to be misleading, anatomically the degree of damage was far more extensive than the roentgenograms indicated. Indriven fragments of bone could not be visualized. The only possible way to do an adequate debridement was by formal laminectomy.



The presence of foreign bodies or indriven bone in the spinal cord sets up a series of pathologic changes, these lesions being similar to those produced by the presence of foreign material in the brain. It was felt that the removal of irritant foreign material prevented the development of cicatrization and further damage to the spinal cord. In addition, laminectomy allowed for repair of the dural defect and the reestablishment of normal circulation in and about the cord.

The following ideas were presented

1 Laminectomy performed by a competent surgeon did not increase either the mortality or the morbidity

2 The long after-care could be more intelligently undertaken if the lesion had been directly observed and recorded

3 The good results in 2 seemingly hopeless cases offered a ray of hope in a depressing situation

4 The presence of immediate complete paralysis did not indicate a hopeless condition

5 Early surgical intervention gave the patient the best possible chance for recovery of any remaining viable spinal cord

#### DISCUSSION

DR PAUL C BUCY Dr Tinsley has presented this tragic picture well. There is probably no field of neurologic surgery in which the surgeon is rewarded so little for his efforts as here, in 2 cases out of 22 there was definite evidence of improvement. But I should agree entirely with Dr Tinsley that in these cases of penetrating wounds of the spine with injury to the spinal cord, and usually with foreign bodies present, early operation with debridement and removal of foreign material is the proper treatment. Any other course of treatment will usually lead to serious, often fatal, infection. However, it should be borne in mind that such an operation will do little to benefit the existing injury to the spinal cord, although it may well prevent further damage from infection and from the reaction to the foreign material. In civilian life, penetrating wounds of the spine are unusual, and, accordingly, there are fewer occasions when there is any indication for an open operation in case of injury to the spine and the spinal cord.

DR HAROLD VORIS I should like to express my admiration of Dr Tinsley's courage in operating in these cases, when it is well known how little one usually can expect in the way of neurologic improvement. I have taken foreign bodies out of the spinal cord in a few cases and can recall only 1 instance in which it was worth while, in that case the body was in the region of the cauda equina, where it is known that the outlook for neurologic recovery is more hopeful. A foreign body in the spinal canal presents a definite indication for removal from the standpoint of sepsis, as has been pointed out, but unless there is actual evidence of foreign material in the spinal canal, surgical intervention is not indicated and from the neurologic standpoint the picture is dismal.

In a case recently under my observation in which there was a bullet wound of the cauda equina, with the bullet lodged anterior to the spine, remarkable improvement occurred without surgical intervention. The patient had been in another hospital for two weeks and was in Cook County Hospital for three or four weeks, he has now graduated to a walker. Perhaps some of the patients who have improved after operation might have done so without surgical treatment. However, there is definite indication for debridement of a compound wound or removal of a foreign body from the spinal cord.

DR MILTON TINSLEY I tried to stress that these were compound spinal wounds. I know that with civilian injuries of the simple fracture type this operative procedure does not hold. However, even though there is no foreign body in the spinal canal, if there is a compound spinal wound with fracture of the laminae, I believe that laminectomy is indicated, to remove any indriven particles that may not be seen in the roentgenogram.

## Cortical Areas of the Albino Rat DR WENDELL J S KRIEG

The identification and arrangement of the cortical areas of the albino rat were determined on the basis of material stained for cells and myelin, sectioned in various planes, reconstructed into a model and illustrated by comparable strips from sections perpendicular to the surface. About forty cortical areas were distinguished and numbered in an attempt to conform to Brodmann's plan.

It was stated that the parietal cortex has been subdivided in a manner that may be more easily equated with that of higher forms. The auditory cortex (41) has been identified, a finding which changes radically the pattern formerly claimed for the lateral region of lower mammals. In the parietal region, distinct areas 3, 1 and 2 occupy a prominent place, while the associative areas 7 and 39 and the temporal associative area are, as was to be expected, smaller. The primary receptive areas dominate the cerebrum. Motor, premotor and frontal areas are distinguished, the last subdivisible into three areas. The limbic lobe is highly developed and presents numerous structural types.

Study of the myelin pattern in the cortex shows distinctions more striking than those in cellular preparations, and these were utilized in delimitation of areas. In the rat many interareal association fibers are found within the cortex, in its lower layers.

The author stated that identification of cortical areas is contingent on the results of the experimental analysis of their connections now in progress.

## DISCUSSION

DR GERHARDT VON BONIN I know only the monkey cortex. The connection between area 17 and the retrosplenial area is apparently common to all mammals. I found it in the macaque, in the chimpanzee and in man.

I was interested to see that the motor area in the rat contains a definite inner granular layer. I have committed myself by stating that this layer is present in primates too. The "postcentral" formations have given rise to doubt in my mind. I am not sure about the extent of the somesthetic areas. Does this whole area receive afferent fibers from the ventromedial nucleus of the thalamus? I am impressed with the extent of area 10. I have not had much experience with the dog and cat brain, but my impression is that the frontal sector is even smaller in these forms than in the rat. I wonder whether Dr Krieg has had any experience with the brains of these carnivores.

The parietal associative areas show a progressive increase in primates. In the macaque there is some differentiation between areas 5 and 7, but areas 39 and 40 are extremely small. Even in the chimpanzee areas 39 and 40, although larger, look similar to each other.

I have studied the macaque and the chimpanzee brains for area 19, and I do not find it. It is impossible to find a clear boundary between area 18 and area 19, despite the fact that some workers have said they could.

Neurologists should be extremely grateful to Dr Krieg for filling the gap in the knowledge of lower mammals and making it unnecessary to rely on the indirect evidence from the mouse, which I have learned to distrust.

DR PERCIVAL BAILEY I was much interested to hear Dr Krieg say he placed so much reliance on myelin studies. I have had the opposite experience. They are so unreliable that I have discontinued them. The slightest variation in length of differentiation alters the picture of the fibers. Also, one might quarrel with the Brodmann scheme of numeration. He did not publish any description of these areas in the human brain and very little in the animal brain. In the monkey brain, on which he made his chief study, he said himself that a great deal of his work was unreliable and that much of his scheme was gratuitous. So my colleagues and I have given up his scheme in favor of that of von Economo and Koskinas, for they have described in great detail what they mean by their subdivisions of the human cortex. Since our ultimate purpose is to understand the human cerebral cortex, we propose to follow the system of von Economo.

Finally, I should like to express my idea of area 2. After reading the descriptions of Brodmann and all the others, I still do not know what is meant by area 2. I cannot get any mental picture of it. I cannot find any zone of constant structure between area 1 and area 5. I do not believe there is any extra area there. There may be in the human brain, although I cannot get any clear picture of it, but certainly not in the macaque. For some of these areas, therefore, I think that such subdivisions as Dr Krieg has made must be accepted with reservations, since Brodmann did not say clearly what he meant by them. In spite of the enormous amount of work done on this matter, the subject is still in its infancy. There is plenty of opportunity to make a plan, the important thing is for all to record accurately and definitely what they mean by the different areas they distinguish, so that any one scheme can be checked with others. This was not done by Brodmann, and for that reason I think it inadvisable to continue to use his scheme as though it were a bible.

DR WENDELL J. S. KRIEG. With respect to area 2 versus area 5, I should be quite willing to accept area 5 in the sense in which it has been defined. It is a parietal area, but it receives the main projection from the ventrolateral region of the thalamus. I want to make it clear that this survey is a preliminary one for my own use, and not primarily for some one in generations to come. The lesions, of which I have about 100, are to be analyzed from the standpoint of these areas. I am quite sure it will be necessary to modify and change my present concept—the lesions are analyzed but not synthesized.

Area 10 is not so large as it appears in the picture, it is small in its medullary aspect. I am not so certain about the partition of the frontal area as I am about other regions.

Dr Bailey's statement about myelin stains is true, one working on monkey brains would take that attitude. But with the rat brain it is different. There are a tremendous number of fibers within the cortex, and if the myelin picture were left out of consideration, one would lose an important source of understanding. My reason for sticking to Brodmann's system is a concession to a large number of people—clinical workers and students who refer to cortical areas by his numbers. If this system can be kept so far as possible, it will save much confusion. My ultimate purpose is the same as that of the Illinois group, to understand the human brain—the over-all picture—and then gradually to add to the anatomic picture.

## Book Reviews

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**Group Psychotherapy. Theory and Practice** By J W Klapman, M D  
Pp 344, New York Grune & Stratton, Inc, 1946

In a field still so fluid and experimental, new books and publications are inevitable. This book has, however, the merit of attempting to lay a theoretic basis for the practice of group psychotherapy, now so popular as a result of military experience. This basis the author finds in the cultural and social heredity of man. He accepts the Cooley-Mead-Dewey-Fariss theory of personality, as expressed in Kingsley Davis' dictum that "human nature is determined by the child's communicationsocial contacts as much as by his organic equipment." Mental disorder from this standpoint may be described in terms of a breakdown in the regulators of social existence. "To integrate them again with the body of the psyche would seem most feasible in the kind of medium where they had their birth." This leads naturally into a discussion of the problems of group transferences and interactions in relation to the dynamics of therapy.

The author reviews briefly the history of group therapy, from the ancient world of King Saul and Socrates to the modern period of the "scientific and conscious use of the medium of group influence." It is of interest to note that the first modern use of the method was with tuberculous patients by Pratt in 1905. The group method of treatment has since been expanded until now it is in use in a wide variety of diseases, both somatic and psychiatric. With psychiatric disorders group therapy has had an equally wide range of expression, from Schilder's intensive work using psychoanalytic concepts through to the repressive-inspirational technics of Alcoholics Anonymous, Inc.

The actual practice of group therapy is discussed with reference to the outpatient clinic, children's guidance clinics (and the mothers of "problem children"), private practice and the large hospital for patients with mental disease. The obvious factors of saving of time and labor, in addition to the problems of size of the group and selection of cases, and the interrelation of individual and group therapy are fully discussed. The author, who is a member of the faculty of Northwestern University Medical School, gives his own methods in a mental disease hospital setting under the general title of "orientative re-educational psychotherapy." According to him, the relation of the intellect to the affect is "a close and reciprocal one," and intellectualization in his groups is therefore not merely superficial. It is dynamic in itself.

The book is somewhat uneven in style, and some of the material, at least, gives evidence of having actually been used in patient groups for "orientative re-education." A more serious fault is the complete omission of cases having an organic background in his discussion of the role of group therapy in psychiatric cases. The book is of value, however, in its many practical suggestions for the actual practice of the method. As an introduction to the subject of group psychotherapy it may be commended.

**Progress in Neurology and Psychiatry An Annual Review** Edited by  
E A Spiegel, M D Price, \$8 Pp 708 New York Grune & Stratton, Inc,  
1946

With this volume, the editor inaugurates a yearly review of advances in neurology and psychiatry. The usefulness and success of the annual reviews in biochemistry and physiology allow one to predict that a counterpart in neurology and psychiatry will gain rapid acceptance.

With the added impetus of wartime research, the assembling of an exhaustive review can be no simple problem. It is gratifying to report that the task is well

done. A vast amount of useful information is contained in this volume, and, in general, controversial issues are presented with objectivity. The sections on psychiatry are splendidly prepared and should prove of great value to the clinician.

If this reviewer might express a wish it would be that editors always conceive it a duty to be frankly critical. The clinician must be given the chance to judge the basic facts of a new concept of therapy. A case in point is the recent interest in the use of neostigmine as a neuromuscular depressant in cases of poliomyelitis, cerebral palsy, rheumatoid arthritis and conditions of the lower part of the back. The physiologic rationale for this widely popularized form of treatment deserves a great deal of discussion by competent authorities. Yet a puzzled clinician might search in vain for a critical survey of the fundamental issue by a respected, objective editor.

Carping over minor errors in proof is admittedly unbecoming, but attention must be called to a rather serious error in the statement, "quinidine hydrochloride has a considerable beneficial effect [in myasthenia gravis]." Also, in the section on surgery of the spinal cord, Scott discusses a case of reverse spondylolisthesis. He describes a patient with complete bilateral spastic paraplegia. This surprising statement then follows: "Laminectomy was considered but not done because the child was able to walk following straightening of the knees and elongation of the Achilles tendon."

Since this volume fills a major need and maintains laudable editorial standards, it is recommended to the student of the fields.

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